National Institute for Public Health
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Ministry of Health, Welfare and Sport

Drugs of abuse and tranquilizers in Dutch

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Results of screening monitoring 2009

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Colophon

This report is published by the National Institute of Public Health and the Environment (RIVM). It describes the results of a screening monitoring campaign on the presence of Drugs of abuse (DOA) in Dutch surface waters and the drinking water that is produced from it. This investigation is carried out by a project group of expertise institutes and coordinated by the RIVM. This investigation took place by order and for the account of VROM-Inspectorate, within the framework of the Programme for Clean and Safe Water, project 703719 Monitoring and Enforcement Drinking Water Act. KWR Watercycle Research Institute, which participated in this study, received financial support from the Joint Research Programme (BTO) of the Dutch water companies. This report is also registrated as BTO 2011.023. The digital version of this report is available on the website of the RIVM (www.rivm.nl).

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Abstract

Drugs of abuse and tranquilizers in Dutch surface waters, drinking water and wastewater
Results of screening monitoring 2009

In the surface waters of the rivers Rhine and Meuse, twelve drugs that are listed in the Dutch Opium act were detected at low concentrations. They are from the groups amphetamines, tranquilizers (barbiturates and benzodiazepines) opiates and cocaine. During drinking water production, most compounds are removed or concentrations are substantially lowered. In finished drinking water, three barbiturates were still detected in very low concentrations (up to 12 ng/L). The amounts are below health based provisional drinking water limits. Ongoing monitoring of the presence of these compounds in water and possible long-term effects on human health are a point of interest. It is recommended to investigate possible ecotoxicological effects.

These findings are the results of a RIVM investigation performed under the authority of the VROM-Inspectorate of the Dutch Ministry of Infrastructure and the Environment. This investigation was carried out in cooperation with KWR Watercycle Research Institute and the Research Institute for Pesticides and Water of the University Jaume I (Spain). A total of 65 water samples were analysed for 37 different drugs of abuse and metabolites. In addition to surface waters and drinking water, sewage waters were also analysed. The compounds can be detected due to the increased sensitivity of analytical methods nowadays available. However, drugs have probably been present in the aquatic environment since they have been used by humans.

Substantial fractions of the total load of drugs in the Rhine and Meuse rivers enter the Netherlands from abroad. There is also a contribution through effluents from sewage water treatment plants in the Netherlands. The concentrations found in Dutch sewage water are in the same range as concentrations found in other Western European countries. Based on the measured concentrations, cocaine consumption in some Dutch cities could be estimated and compared.

Keywords:
Drugs of abuse, drinking water, surface water, sewage treatment plants, monitoring

Rapport in het kort

Drugs en kalmeringsmiddelen in Nederlands oppervlaktewater, drinkwater en afvalwater
Resultaten van verkennende metingen 2009

In oppervlaktewater van de Rijn en de Maas zijn lage concentraties aangetoond van twaalf stoffen die zijn opgenomen in de Opiumwet. Het gaat om stoffen uit de groepen amphetaminen, slaap- en kalmeringsmiddelen (barbituraten en benzodiazepinen) opiaten en cocaïne. De meeste van deze stoffen worden verwijderd of sterk in concentratie verlaagd tijdens de drinkwaterzuivering. In het drinkwater worden uiteindelijk nog drie stoffen aangetroffen, allen barbituraten. De concentraties zijn zeer laag (maximaal 12 nanogram per liter). Hiermee worden de gezondheidskundige risiconormen voor drinkwater niet overschreden. Het is raadzaam om de aanwezigheid van deze stoffen in het watersysteem te blijven volgen met het oog op mogelijke effecten op de volksgezondheid op lange termijn. Daarnaast wordt aanbevolen om de mogelijke effecten op het ecosysteem te onderzoeken.

Dit blijkt uit onderzoek van het RIVM, in opdracht van de VROM-Inspectie van het ministerie van Infrastructuur & Milieu. Het onderzoek is uitgevoerd in samenwerking met KWR Watercycle Research Institute en het Research Institute for Pesticides and Water van de Spaanse Universiteit Jaume I. In totaal zijn 65 watermonsters onderzocht op de aanwezigheid van 37 verschillende drugs en afbraakproducten. Behalve oppervlaktewater en drinkwater is ook stedelijk afvalwater onderzocht. De aangetroffen stoffen konden worden opgespoord dankzij geavanceerde meettechnieken die sinds kort beschikbaar zijn, maar zijn waarschijnlijk al aanwezig in het watersysteem sinds mensen ze gebruiken.

Een substantieel deel van de onderzochte stoffen in de Maas en Rijn komt vanuit het buitenland. Vervolgens draagt ook het afvalwater van rioolwaterzuiveringsinstallaties in Nederland hieraan bij. De gevonden concentraties in Nederlands afvalwater zijn van dezelfde ordegrootte als de concentraties in andere West-Europese landen. Met behulp van de gemeten concentraties was het mogelijk om de cocaine consumptie in een aantal steden te schatten en met elkaar te vergelijken.

Trefwoorden:
drugs, drinkwater, oppervlaktewater, rioolwaterzuiveringsinstallaties, monitoring

Acknowledgements

We thank the employees of the Dutch drinking water companies and the sewage water treatment plants who supported our monitoring campaign. The assistance of Bert van Dijk and Frank Weijs (RIVM) who performed the sampling, Tibor Brunt (Trimbos Institute) who assisted in the selection of the STP monitoring locations and Jessica van Montfoort (RIVM) who provided information on prescription drugs is also gratefully acknowledged.

Contents

Summary

Drugs of abuse (DOA) and their degradation products have recently been recognised as emerging environmental contaminants. They are among the growing number of compounds that is detected in the water environment, which is among other things related to the increasing sensitivity of analytical methods. DOA refers to both illegal drugs and the (illegal) misuse of prescription drugs such as tranquilizers and are listed in the Dutch Opium act.

Objectives

The Inspectorate of the Dutch Ministry of Infrastructure and the Environment asked the National Institute for Public Health and the Environment (RIVM), to perform a screening monitoring in the Netherlands. The screening was carried out in close cooperation with the joint research programme (BTO) of the Dutch water companies, executed by KWR Watercycle Research Institute. The focus of interest is the question of whether DOA are present in Dutch surface waters and the drinking water that is produced from it. The main objectives pursued within this study were:

- to evaluate the occurrence of DOA and metabolite residues in the Dutch surface waters that are important resources for drinking water production
- to evaluate the occurrence of DOA in raw water and finished drinking water that is produced from surface water or bank filtrate
- to perform a risk assessment on human health in case DOA are detected in drinking water
- to evaluate the occurrence of DOA and metabolite residues at some Dutch sewage treatment plants (STPs) that discharge their effluents into the Rhine and Meuse rivers.

Design of sampling campaign

A total of 37 DOA and metabolites belonging to 7 different chemical classes were selected. Most of the compounds selected are listed in the Dutch Opium act as List I or List II substances. The sampling campaign was performed between October 4th and November 1st of 2009. At the STP, 24-hour flow dependent samples from influent and effluent were taken on weekend days. The water samples were analysed by three laboratories: RIVM, KWR Watercycle Research Institute and the Research Institute for Pesticides and Water of the University Jaume I (Spain). Some of the STP wastewater samples were also analysed by the University of Antwerp. Samples were collected from 65 sites, which can be characterised into three types of water:

- *Surface waters*

  Samples were taken at all nine surface water intake points for drinking water production in the Netherlands. Eight of these locations are part of the Meuse and Rhine river basins, and one is part of the Ems river basin. Samples were also taken at five additional locations along the rivers Rhine and Meuse which are part of the national monitoring network of the Directorate for Public Works and Water Management.
- *Raw water and finished drinking water*

  At ten production sites where drinking water is produced from surface water, samples were taken from the raw water and from the finished drinking water. In addition, samples were taken from the raw water and finished drinking water at seven drinking water production sites, where drinking water is produced from bank filtration.

- *Urban wastewater*

At eight STPs samples were taken from both the influent and effluent water.

Results for surface waters and drinking water

In the surface waters of the rivers Rhine and Meuse, 12 out of the total number of 35 compounds investigated were detected in concentrations up to 68 ng/L:

- the amphetamine-type stimulants methamphetamine and MDMA (Ecstasy)
- cocaine and its major metabolite benzoylecgonine
- the opiates codeine, morphine and methadone
- the barbiturates pentobarbital, phenobarbital and barbital
- the benzodiazepines oxazepam and temazepam

Phenobarbital, oxazepam, temazepam and benzoylecgonine were most abundantly present: at > 70% of the total of 14 surface water sampling locations.

In raw water, 6 out of the total number of 35 compounds investigated were detected at concentrations up to 27 ng/L:

- the barbiturates pentobarbital, phenobarbital and barbital
- the benzodiazepines oxazepam and temazepam
- benzoylecgonine

In finished drinking water, 3 out of the total number of 35 compounds investigated were detected: the barbiturates pentobarbital, phenobarbital and barbital, at concentrations up to 12 ng/L. Benzoylecgonine, the main metabolite of cocaine, was detected in one finished drinking water sample but in a concentration < Limit Of Quantification (LOQ) of 1 ng/L. From the 17 finished drinking water samples, 6 samples (35%) contained one or more barbiturates ≥ LOQ. When also the monitoring results < LOQ (2–4 ng/L) are taken into account, 13 samples (76%) contained one or more barbiturates. Phenobarbital is detected most frequently, followed by barbital and pentobarbital.

Drinking water treatment

The amphetamine-type stimulants, cocainics and opiates that are present at the river water intake points are not present in the raw water. The raw water also contains reduced concentrations of oxazepam, temazepam, benzoylecgonine and phenobarbital compared to their concentrations detected at the river water intake points. Apparently, these compounds are removed to some extent during reservoir storage, pre-treatment or soil aquifer recharge that take place between river water intake point and raw water sampling location. Benzodiazepines are not detected in the raw water that is produced from bank filtrate: possibly they have been removed during bank filtration.

Barbiturates appear only to get partly removed during drinking water treatment. Pentobarbital and barbital were detected more frequently in raw water and finished drinking water that is produced from bank filtrate than in raw water and finished drinking water that is produced from surface water. The presence of barbital might be related to the greater share of older groundwater in bank filtrate. This might be the reason why barbital, a tranquilizer that has been used as a human medicine since the beginning of the 20th century but is no longer available as a prescription drug, is still detected.

Urban wastewater

Out of the total number of 37 compounds investigated, 18 compounds were detected in STP influents and 25 compounds in STP effluent samples. Most compounds detected in the STP influent were also detected in the STP effluent, except for the cannabinoid THC-COOH and a metabolite of cocaine (Cocaethylene). Compounds from all chemical groups except the cannabinoids were present in STP effluents: amphetamines, barbiturates, benzodiazepines, cocainics, opiates and others. Concentrations of drugs and metabolites were mostly lower in effluents than influents, suggesting degradation or sorption of these substances and metabolites in wastewater treatment plants. Concentrations in the Dutch STPs are mostly of the same order of magnitude as monitoring data that were acquired during other studies in Spain, UK and Italy.

Comparison with provisional drinking water limits

The concentrations of the DOA detected in drinking water are far below the general signal value of 1 µg/L, which is specified for organic compounds of anthropogenic origin in the Dutch Drinking water act. For individual DOA, no statutory drinking water standars are available. Therefore health based provisional drinking water limits were derived in this study, based on currently available toxicological knowledge. For the three barbiturates that are detected in finished drinking water, the provisional drinking water limit is about 1800 times higher than the actual concentrations detected. Based on this information, effects on public health are not expected. However, little is known about the possible effects of combined exposure to multiple compounds at low concentrations. Long-term effects on organisms in the aquatic environment like rivers are also less clear.

Loads of DOA through rivers and wastewater and origin of the compounds

Substantial fractions of the total load of drugs in the Rhine and Meuse rivers enter the Netherlands from abroad. At Lobith, the load of oxazepam is highest and comparable to the loads of other broadly used pharmaceuticals, such as antibiotics. For some compounds loads seem to increase downstream, which is probably caused by a contribution from STP effluents.

For phenobarbital, a compound that is clearly difficult to remove during treatment, prescription use is probably an important source besides possible 'abuse' of this so-called soft drug that is listed as a List II substance in the Dutch Opium act. Prescription uses is also an important source for the benzodiazepins oxazepam and temazepam which were among the top10 of most prescribed pharmaceuticals in the Netherlands in 2007 and 2008.

Based on the measured concentrations for benzoylecgonine, cocaine consumption could be estimated for eight Dutch towns. The results show a variable level of drug consumption which is within the range of cocaine consumption for Belgian cities as estimated in other studies.

Recommendations

Although there is no indication of human health risks with respect to the compounds detected in finished drinking water, alertness is required. Ongoing research with respect to possible effects of combined exposure to multiple compounds at low concentrations needs attention, as well as the development of analytical techniques to detect possible new emerging contaminants.

As this first screening monitoring campaign was limited, a more thorough monitoring yielding information on statistical uncertainty and variability in time and space is recommended. In order to be able to better evaluate the presence of DOA in these waters, a more thorough derivation of human and ecotoxicological health standards for DOA in surface waters and drinking water is required.

An ecotoxicological risk assessment of DOA in the aquatic environment is recommended, especially at locations where these DOA are discharged into surface waters through STP effluents. Further research is recommended to investigate the contributions of STPs with respect to amounts of DOAs that are discharged into surface waters and the rivers Rhine and Meuse, what kinds of processes occur within the STP, their effects on the fate of the compounds and concentrations in STP effluents.

Further research into the presence of barbiturates in drinking water will help determine the necessity of adaptation measures. Information on effectiveness of drinking water treatment, sources and pathways will help focus possible adaptation measures.

1 Introduction

Drugs of abuse (DOA) and their degradation products have recently been recognised as environmental emerging contaminants. They are among the growing number of compounds that is detected in the water environment, which is related to the increasing sensitivity of analytical methods. DOA refers to both illegal drugs and the misuse of prescription drugs such as tranquilizers. DOA have received increased interest since Jones-Lepp et al. (2004) first reported their occurrence in treated sewage effluents in the US. Following consumption, DOA and their metabolites are continuously released into the aquatic environment due to their partial elimination in sewage treatment plants (STPs). Recent studies have shown the occurrence of DOA and their metabolites in STPs and river water in the US (Vanderford and Snyder, 2006; Bartelt-Hunt et al., 2009) and in European countries like Italy and Switzerland (Zuccato et al., 2005; Zuccato et al., 2008; Castiglioni et al., 2006), Spain (Boleda et al., 2007; Huerta-Fontela et al., 2007; Postigo et al., 2008; Bijlsma et al., 2009; Huerta-Fontela et al., 2008), United Kingdom (Kasprzyk-Hordern et al., 2007), Ireland (Bones et al., 2007), Germany (Hummel et al., 2006) and Belgium (Nuijs et al., 2009). Possible ecotoxicological and human toxicological effects of their presence in the aquatic environment have not been investigated so far.

Besides the objective of monitoring their environmental occurrence, several authors have developed analytical methodologies to determine DOA and their metabolites in water matrices with the objective to estimate collective drug consumption at the community level (Daughton and Jones-Lepp, 2001; Zuccato et al., 2005; Zuccato et al., 2008). According to Nuijs et al. (2009; 2009b) wastewater analysis is a promising tool to evaluate cocaine consumption at both local and national scales.

In the Netherlands, little is known about the occurrence of DOA and their degradation products in the water environment. An exploratory study on the occurrence of DOA in Dutch surface waters and STP effluents was conducted in 2006–2007 by the KWR Watercycle Research Institute (Kiwa Water Research at that time). At one STP effluent and four surface water sampling locations, at least 4 out of the 14 DOA investigated were detected (Deltalab 2007; Hogenboom et al., 2009; De Voogt et al., in press). These included opioids, benzoylecgonine (human metabolite of cocaine), methadone and two tranquilizers, nordazepam and oxazepam. However, concentration levels could not be calculated since at that time no license to order, store and analyse these types of drugs was available.

The Dutch Ministry for Housing, Spatial Planning and the Environment (VROM) asked the National Institute of Public Health and the Environment (RIVM), to perform a screening monitoring in the Netherlands. This screening was carried out in close cooperation with the joint research programme (BTO) of the Dutch water companies, executed by KWR Watercycle Research Institute. The focus of interest in this first screening monitoring campaign is the question of whether DOA are present in Dutch surface waters and the drinking water that is produced from it

The main objectives pursued within this study were:

1. to evaluate the occurrence of DOA and metabolites residue in Dutch surface waters that are important resources for drinking water production

2. to evaluate the occurrence of DOA in raw water and finished drinking water that is produced from surface water or bank filtrate
3. to perform a risk assessment on human health in case DOA are detected in drinking water
4. to evaluate the occurrence of DOA and metabolites residue at Dutch STPs that discharge their effluents into the Rhine and Meuse rivers

The sampling campaign in this study was performed by RIVM. The water samples were analysed by three laboratories: RIVM, KWR Watercycle Research Institute and University Jaume I. Some of the STP wastewater samples were also analysed by the University of Antwerp. This made it possible to cover a broad range of compounds and compare results.

2 Methods and materials

2.1 Selection of sampling locations

Figure 2.1 presents an overview of the sampling locations. Samples were collected from 65 sites that can be characterised into three types of waters:

1. *Surface waters*
   Samples were taken at all nine surface water intake points for drinking water production in the Netherlands. Eight of these locations are part of the Meuse and Rhine river basins, one is part of the Ems river basin. In addition, samples were taken at five locations along the Rhine and Meuse which are part of the national monitoring network of the Dutch Directorate General of Public Works and Water Management (Rijkswaterstaat -RWS).
2. *Raw water and finished drinking water*
   At ten production sites where drinking water is produced from surface water, samples were taken from the raw water (before it enters the drinking water treatment plant)[1] and from the finished drinking water. In addition, samples were taken from the raw water and finished drinking water at seven drinking water production sites where drinking water is produced from bank infiltration.
3. *Urban wastewater*
   At eight STPs, samples were taken from both the influent and effluent water. The size of these conventional biological treatment plants varies from 37,000 to 1 million equivalent-inhabitants. The STPs are located along the rivers Rhine and Meuse or serve cities considered important for estimating drug usage at the community level.

2.2 Selection of compounds

A total of 37 DOA and metabolites belonging to 7 different chemical classes were selected (Table 2.1). Most of the compounds selected are listed in the Dutch Opium act as List I or List II substances. List I refers to so called "hard drugs" which are generally assumed to pose an unacceptable human health risk. List II refers to legal but addictive drugs or so-called "soft drugs" which in general pose a smaller human health risk. The following selection criteria were taken into consideration:

- Estimated consumption of DOA in the Netherlands (National Drug Monitor Jaarbericht, 2006), which is published by the Trimbos Institute (Netherlands Institute of Mental Health and Addiction). In this report, the illicit drug consumption is estimated based on criteria such as (il)legal import volumes and anonymous surveys.

[1] At some production sites the surface water has undergone pre-treatment, like for example direct filtration, subsoil passage in the dune areas or storage in a reservoir before it enters the drinking water treatment plant.

- Results of a preliminary inventory study on the occurrence of DOA in Dutch surface waters and STP effluent water (Deltalab, 2007; Hogenboom et al., 2009; De Voogt et al., in press).
- International occurrence data on DOA in the water environment (e.g., Huerta-Fontela et al., 2007; Bijlsma et al., 2009)
- Availability of standards, internal standards and analytical methods at the different laboratories

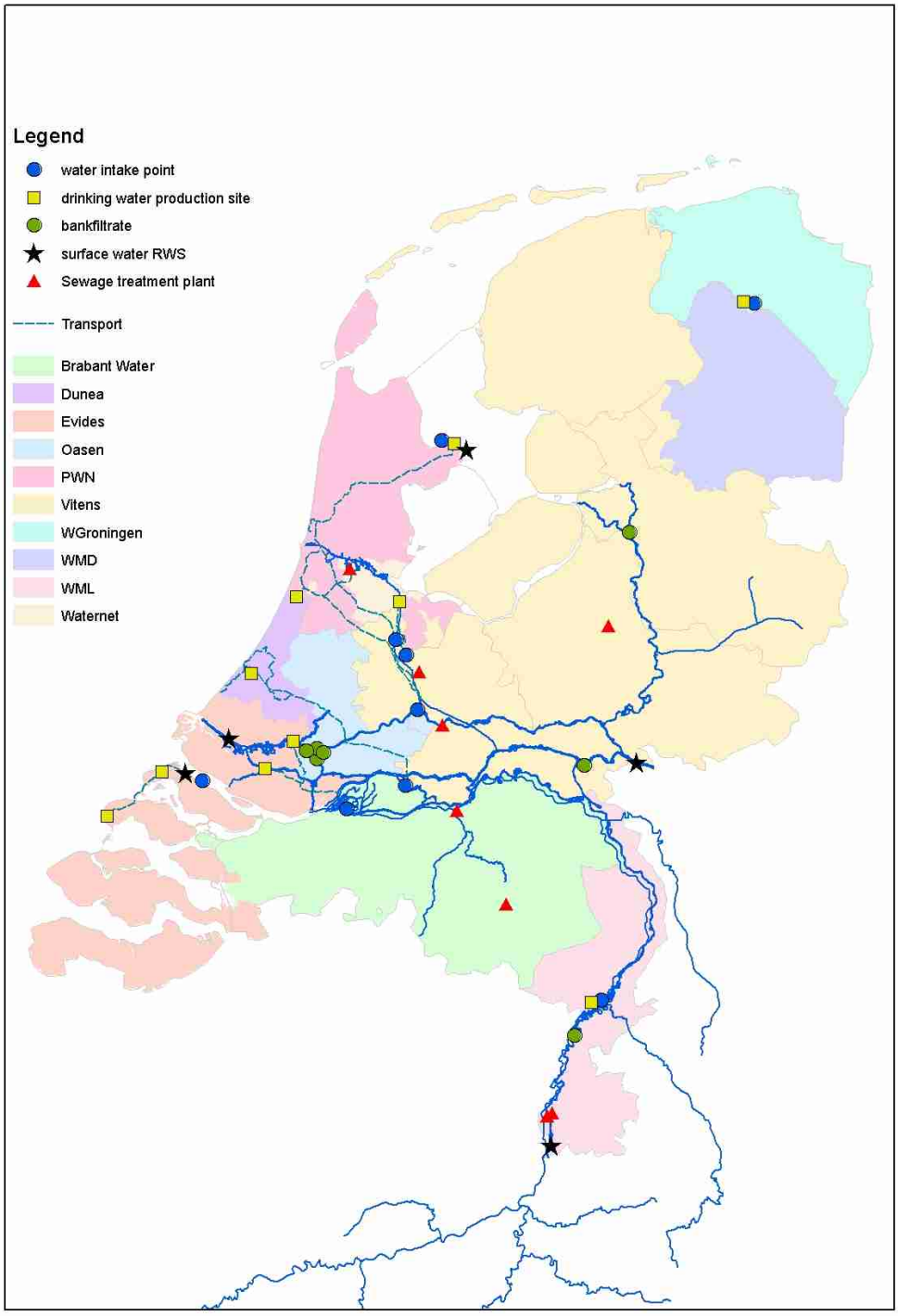

Figure 2.1. Overview of sampling locations of the monitoring campaign on DOA in Dutch waters. Coloured regions correspond to water suppliers.

Table 2.1. Overview of the DOA analysed by the four participating laboratories

Chemical class	Compound	Relation to parent drug	Log Kow [a]	Opium act	Analyzed by laboratory			
					UJI	RIVM	KWR	UA
Amphetamines	amphetamine	major excretion product	1.81	List I				
	metamphetamine	major excretion product	1.94	List I				
	MDA		1.67	List I				
	MDMA (Ecstasy)	major excretion product	1.81	List I				
	MDEA		2.34	List I				
Barbiturates	pentobarbital (also aneasthetic) *	also main metabolite of thiopental		List II				
	phenobarbital *	also main metabolite of primidone	1.47	List II				
	barbital		0.65	List II				
Benzodiazepins	diazepam *		2.9	List II				
	nordazepam (desmethyl-diazepam)	metabolite of diazepam	3.15	List II				
	oxazepam *	also metabolite of diazepam	2.31	List II				
	temazepam *	also metabolite of diazepam	2.15	List II				
	desalkylflurazepam	metabolite of flurazepam	3.02	List II				
	flunitrazepam (rohypnol) *			List II				
Cannabinoids	11-nor-9-Carboxy-THC (THC-COOH)	major metabolite of THC	6.21	List I				
	11-OH- Δ-9-THC	metabolite of THC	6.58	List I				
	Δ-9-THC	metabolite of THC	7.68	List I				
Cocainics	cocaine	parent drug, minor excretion product	3.08	List I				
	benzoylecgonine (BE)	major metabolite of cocaine	2.72	List I				
	cocaethylene (CE)	metabolite of cocaine		List I				
	norbenzoylecgonine	metabolite of cocaine		List I				
	norcocaine	metabolite of cocaine		List I				
	ecgonine methyl ester	metabolite of cocaine		List I				
Opiates	fentanyl * (also anaesthetic)		3.89	List I				
	heroin		1.52	List I				
	6-monoacetyl morphine (6-MAM)	minor but exclusive metabolite of heroin	1.32	List I				
	morphine * (also anaesthetic)	major but non-exclusive matbolite of heroin	0.43	List I				
	codeïne *		1.2	List I				
	methadon *			List I				
	EDDP	metabolite of methadon	5.51	List I				
Others	ketamine (also aneasthetic)		2.28					
	meprobamate *		0.7	List II				
	mCPP (Meta-chlorophenylpiperazine)	also major metabolite of tradozone	2.07					
	methcathinone		1.4	List II				
	ritalin / methylphenidate*		2.55	List I				
	phencyclidine (PCP)			List II				
	LSD			List I				

* also currently available as a prescription drug.

[a] partition coefficient n-octanol/water.

Some of the compounds in Table 2.1 are currently also available as prescription drugs. This applies to some opiates and tranquilizers: meprobamate and the benzodiazepines are tranquilizers that are prescribed by physicians for anxiety and sleeping problems. Barbital and meprobamate have mostly been replaced by benzodiazepines since these were introduced in the 1960s. The benzodiazepins oxazepam and temazepam were among the top10 of most prescribed pharmaceuticals in the Netherlands in 2007 and 2008 (SFK, 2007; 2008) Phenobarbital has been internationally available as a prescription drug since 1912 and is still used for epileptic disorders. In the Netherlands, barbital is not available as a prescription drug any longer. Besides phenobarbital, the barbiturates that are most frequently used, thiopental and pentobarbital, are also prescribed in the Netherlands (for cerebral oedema and euthanasia). Thiopental and pentobarbital are also used as veterinary medicine.

Table 2.1 shows the Log Kow (partition coefficient n-octanol/water). Substances with relatively low n-octanol/water partition coefficients are very hydrophilic ("water-loving") and in general more difficult to remove during treatment, especially in treatmentsteps involving sorption Table 2.1 shows that the substances with relatively low Log Kow (≤ 1.5) are phenobarbital, barbital,

heroin, 6-monoacetyl morphine (6-MAM), morphine, codeine, meprobamate and methcathinone. The cannabinoides show the highest Log Kow (6–7).

2.3 Sample collection

Samples were collected between October 4th and November 1st of 2009. At each sampling location for surface water and drinking water, grab samples were collected and bottles were filled for each of the three laboratories: 250 ml in glass bottles for both UJI and RIVM, 1 litre in a glass bottle for KWR. At the drinking water production sites, both the raw water and finished drinking water were sampled on the same day, without accounting for lag-time. Likewise, both the influent and effluent at every STP were sampled on the same day. At the STP, 24-hour flow dependent samples from influent and effluent were taken on weekend days in 1 litre glass bottles for each of the four laboratories. The samples were transported and stored in the dark at 5 °C.

2.4 Analytical methods

Table 2.2 shows an overview of the main characteristics of the analytical methods used by the four laboratories that participated in this survey. The mass spectrometric technique used was triple quadrupole except for KWR, who were using a LTQ-Orbitrap (high-resolution mass spectrometry) Further details and instrument parameters can be found in Appendices A to D.

Table 2.2. Summary of the analytical methods used by the four laboratories

	Sample intake (ml)	Pre-treatment	pH adjust-ment	SPE column	Anal HPLC column	Final volume extract (µl)	Injected (µl)	Amount of sample analysed (ml)	Conc. factors
RIVM	100 (STP infl 20)	none	No	HLB	C18	400	25	6.25 (STP infl 1.25)	250 (STP infl 50)
KWR	900	filtration	pH 7.0	HLB	C18	500	20	36	1800
UJI	50 (STP infl 10)	Centri-fugation	pH 2	MCX	C18	1000	20	1 (STP infl 0.2)	50 (STP infl 10)
UA	50	filtration	pH 2	MCX	HILIC	200	5	1.25	250

Most of the laboratories filter their samples before extraction, which can lead to unwanted adsorption of the more apolair analytes that are more prone to adsorption. Only one laboratory (UJI) uses centrifugation, which can also lead to adsorption to the pellet but to a lesser extent. The main differences between the laboratories are the concentration steps and the amount of sample analysed (Table 2.2).

KWR has by far the highest concentration factor, followed by UA, RIVM and UJI. The high concentration factor for KWR is necessary due to the sensitivity of the Orbitrap-FTMS, which is roughly a factor 5–10 less sensitive, depending on the compound. The drawback of the high concentration factor is the amount of possible co-extracted matrix compound that can potentially interfere.

The addition of appropriate internal standards is one of the best approaches to compensate for matrix effects, especially when using analyte isotope labelled internal standard, as one expects that the internal standard is affected by matrix effects in the same way as the analyte. When the internal standard is used as surrogate (i.e., added to the sample prior to sample treatment), it can also compensate for potential analytical errors associated with sample manipulation (Bijlsma et al., 2009).

2.4.1 Identification and confirmation

Compound identification and confirmation is of great importance in order to avoid the reporting of false positives. This is especially true when analysing DOA at trace levels in complex matrices. One of the most frequently used confirmation criteria is based on the concept of identification points (EC, 2002) which are earned depending on the mass analyser used. For low resolution triple quadrupole (QqQ) instruments, as used by the RIVM, UJI and UA, a minimum of two Selected Reaction Monitoring (SRM) transitions were monitored for a safe positive finding, together with the measurement of the ion ratio between both recorded transitions. The retention times of the compounds were compared to those of the compounds in the calibration standard solution of the final analysis. For confirmation of target compounds, LC relative retention time criteria (retention time window < 2.5%) need to be fulfilled. All developed methods comply with these criteria.

For the LTQ FT Orbitrap MS–MS at KWR, the identification is different and was performed by accurate mass of the protonated molecule (or deprotonated in negative mode) within a narrow relative mass window of 5 ppm. Simultaneously, nominal product mass spectra were acquired (LTQ) from the protonated molecule and used for final confirmation. While the mass spectrometric identification criteria for accurate mass screening using high resolution and accuracy instruments are not described (EC, 2002), a proposal was made for high-resolution instruments by Nielen et al. (2007). For high-resolution screening (resolution > 20,000 and a mass accuracy ≤ 5 mDa) these authors proposed
two identification points. Combining this with the nominal product ion, a total of 3.5 identification points are achieved, thus meeting the requirement of three points for confirmation of veterinary drugs and contaminants. The barbiturates in drinking water were confirmed by using a combination of accurate mass of the deprotonated molecule and a high mass accuracy product ion, resulting in a total of four identification points.

2.4.2 Limit of quantification

The limit of quantification (LOQ) is the concentration at which quantitative results can be reported with a high degree of confidence. The LOQ is higher than the LOD (Limit of Detection), the point at which analysis is just feasible but where there is greater uncertainty involved. LOQs are sample-matrix dependent and are therefore presented separately for the surface water and drinking water samples, the influent samples and the effluent samples. LOQs are also dependent on the analytical procedure and therefore differ among the four laboratories. The methods of determining the LOQ at the different laboratories are described in Appendices A to D.

Table 2.4 shows an overview of the LOQs for each compound, sample matrix and laboratory. Since LOQs are highly dependent on the matrix water

composition and on instrument sensitivity conditions, the LOQs given should be taken as estimated values because some variations could be observed along the analysis of samples. For the drinking and surface water samples, seven compounds were analysed by all three laboratories, so the LOQs can be compared. These compounds are amphetamine, methamphetamine, MDA, MDMA, MDEA, cocaine and benzoylecgonine (BE). For most of the compounds, KWR had the lowest LOQs. Their LOQs are on average about three times lower than the LOQs of RIVM for the same compound, and eight times lower than the LOQs of UJI. Besides the difference in analytical instruments, this is probably also partly caused by the difference in concentration step, which is highest at KWR and lowest at UJI (Table 2.3).

For the STP influent and effluent samples, five compounds were analysed by all four laboratories: amphetamine, methamphetamine, MDMA, cocaine and benzoylecgonine (BE). For all compounds UA had the lowest LOQ, although UA uses a lower concentration step than KWR (Table 2.3). The analytical separation method of UA uses a different approach for separating the compounds in the HPLC by means of HILIC. This method has the ability to separate the matrix interferences more efficiently**.** In the STP influent samples, the UA LOQs are on average 19 times, 100 times and 59 times lower than the LOQs of resp. KWR, RIVM and UJI for the same compounds. In the STP effluent samples, the differences are smaller: UA LOQs are on average two times, ten times and twelve times lower than the LOQs of resp. KWR, RIVM and UJI for the same compounds.

Table 2.4. Overview LOQs (ng/L) per compound, sample matrix and laboratory

Chemical class	Compound	Drinking + surface water			STP influent				STP Efluent			
		RIVM	KWR	UJI	RIVM	KWR	UJI	UA	RIVM	KWR	UJI	UA
Amphetamines	amphetamine	5	1	10	116	42	87	2	22	2	46	2
	metamphetamine	3	1	15	23	19	152	1	9	1	19	1
	MDA	5	2	17	324	63	160		22	2	56	
	MDMA (Ecstasy)	2	2	10	41	48	76	1	11	3	9	1
	MDEA	2	1	13	46	63	154		3	2	37	
Barbiturates	pentobarbital		2			18				2		
	phenobarbital		4			44				6		
	barbital		4			44				6		
Benzodiazepins	diazepam		1			2				1		
	nordazepam (desmethyl-diazepam)		1			4				2		
	oxazepam		1			2				1		
	temazepam		1			4				2		
	desalkylflurazepam		1			1				n/b		
	flunitrazepam (rohypnol)	4			106				18			
Cannabinoids	11-nor-9-Carboxy-THC (THC-COOH)		10			152				28		
	11-OH- Δ-9-THC		22			131				13		
	Δ-9-THC		2375			2375				2375		
Cocainics	cocaine	4	1	3	57	3	9	1	7	2	3	1
	benzoylecgonine (BE)	2	1	2	323	5	12	1	14	2	6	1
	cocaethylene (CE)			1			6				3	
	norbenzoylecgonine			6			10				3	
	norcocaine			7			31				3	
	ecgonine methyl ester							2				2
Opiates	fentanyl	3	n/b		417	4			4	2		
	heroin		1			5				3		
	6-monoacetyl morphine (6-MAM)		1			2		1		1		1
	morphine		1			4				2		
	codeïne		1			2				1		
	methadon		1			2		1		1		1
	EDDP							1				1
Others	ketamine	2	1		51	4			8	2		
	meprobamate		n/b			n/b				n/b		
	meta-CPP		1			5				2		
	methacathinone		1			42				2		
	ritalin / methylphenidate		1			5				2		
	phencyclidine (PCP)	1			141				6			
	LSD	10			135				14			

n/b = unable to determine

3 Results and discussion

3.1 Surface waters and drinking water

The monitoring results for surface waters and drinking water are summarised in Table 3.1. The complete monitoring results from the three different laboratories are shown in Appendix E. Monitoring results ≥ LOQ are presented. KWR is the only laboratory for which monitoring results are also presented if <LOQ but >LOD. This is related to the analytical instrument used by KWR (as explained in Appendix C). Whenever there is a signal confirmed, the compound is present and reported. However, results <LOQ are only qualitatively presented because the uncertainty involved is considered too big.

Table 3.1. Summary of frequency of detection of DOA in Dutch surface waters, raw water and finished drinking water

Chemical class	Compound	Surface water (n= 14)		Raw drinking water (n=17)		Finished drinking water (n=17)	
		≥ LOQ (%)	conc. range	≥ LOQ (%)	conc. range	≥ LOQ (%)	conc. range
Amphetamines	metamphetamine	1 (7%)	1 ng/l	-		-	
	MDMA	2 (14%) *e	2 ng/l	-		-	
Barbiturates	pentobarbital	1 (3%) *a	4 ng/l	5 (29%) *b	3-10 ng/l	3 (18%)	4-6 ng/l
	phenobarbital	13 (93%)	7-27 ng/l	10 (59%) *c	6-27 ng/l	5 (29%) *d	5-12 ng/l
	barbital	2 (14%) *e	7-12 ng/l	7 (41%)	5-13 ng/l	4 (24%) *d	4-9 ng/l
Benzodiazepins	oxazepam	12 (86%)	6-68 ng/l	7 (41%)	3-13 ng/l	-	
	temazepam	12 (86%)	3-32 ng/l	7 (41%)	1-10 ng/l	-	
Cocainics	cocaïne	2 (14%)	1-3 ng/l	-		-	
	benzoylecgonine (BE)	10 (71%)	1-16 ng/l	5 (29%)	1-3 ng/l	- *f	
Opiates	codeïne	7 (50%) *g	1-23 ng/l	-		-	
	morphine	1 (7%)	7 ng/l	-		-	
	methadon	3 (21%) *h	1-2 ng/l	-		-	

*a detected in 3 other surface water samples but not quantified because below LOQ (2 ng/L)

*b detected in 2 other raw water samples but not quantified because below LOQ (2 ng/L)

*c detected in 3 other raw water samples but not quantified because below LOQ (4 ng/L)

*d detected in 5 other finished drinking water samples but not quantified because below LOQ (4 ng/L)

*e detected in 2 other surface water samples but not quantified because below LOQ (4 ng/L)

*f detected in 1 finished drinking water sample but not quantified because below LOQ (1 ng/L)

*g detected in 1 other surface water sample but not quantified because below LOQ (1 ng/L)

*h detected in 9 other surface water samples but not quantified because below LOQ (1 ng/L)

Out of the total number of 35 DOA and metabolites analysed, 12 compounds were detected in surface waters, 6 were detected in raw water and 3 in finished drinking water. Benzoylecgonine (BE) was detected in one finished drinking water sample but in a concentration too low to quantify (< LOQ but > LOD). The 3 compounds detected ≥ LOQ are the 3 barbiturates (pentobarbital, phenobarbital and barbital) which were detected in 18–29% of the finished drinking water samples. From the 17 finished drinking water samples, 6 samples (35%) contained one or more barbiturates ≥ LOQ. When the monitoring results < LOQ of 2-4 ng/L are also taken into account, 13 samples (76%) contained one or more barbiturates. Phenobarbital is detected most frequently, followed by barbital and pentobarbital.

3.1.1 *DOA in the drinking water treatment chain*

Figure 3.1 shows average concentrations of DOA for the three drinking water sources that were sampled: surface water with soil aquifer recharge, surface water with direct treatment and bank filtrate. The drinking water treatment techniques can differ between these three production types. The monitoring results are not directly suitable to evaluate the effectiveness of the different treatment steps, since both the raw water and finished drinking water were sampled only once, on the same day and without accounting for lag-time. However, Figure 3.1 presents a visualisation of compounds that are able to pass drinking water treatment.

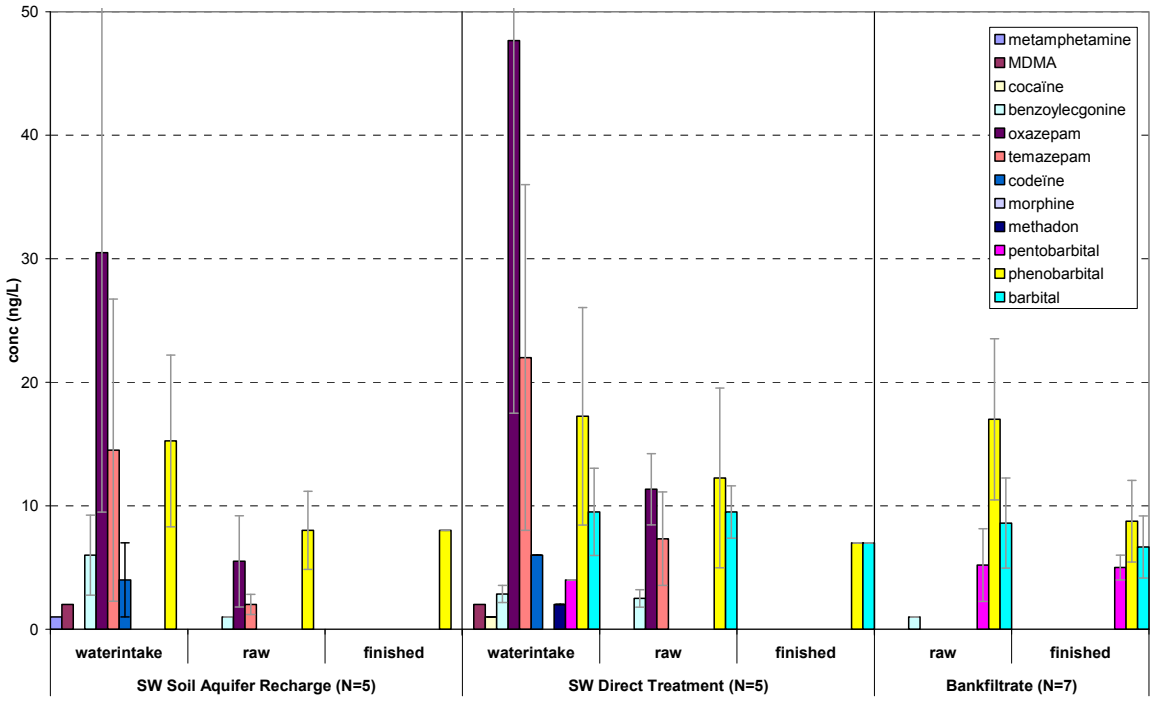

Figure 3.1. Average concentrations of DOA (ng/L) with SD for the three drinking water production types

Figure 3.1 shows that the amphetamine-type stimulants, cocainics and opiates that are present at the river water intake points are not present in the raw water. The raw water (after reservoir storage or soil aquifer recharge) also contains lower concentrations of oxazepam, temazepam, benzoylecgonine and phenobarbital compared to their concentrations detected at the river water intake points. Apparently, these compounds are removed to some extent during reservoir storage, pre-treatment or soil aquifer recharge. Benzodiazepines are not detected in the raw water that is produced from bank filtrate: possibly, they have been removed during bank filtration. Benzodiazepines are not detected in finished drinking water and benzoylecgonine is detected in one finished drinking water sample in a concentration <LOQ (1 ng/L). Apparently drinking water treatment, which mostly consists of a combination of coagulation/flocculation and filtration/flotation, UV or ozonation followed by activated carbon filtration, is effective. This is in agreement with the results of Huerta-Fontela et al. (2008). In their study on the removal efficiency of Spanish drinking water treatment plants, amphetamine-type stimulants were completely removed during pre-

chlorination, flocculation and sand filtration steps, yielding concentrations lower than their limits of detection (LODs). Although in their study reductions of 90% for benzoylecgonine were obtained, benzoylecgonine was still detected in most finished waters at mean concentrations of 45 ng/L.

Barbiturates only get partly removed during drinking water treatment This is probably related to the fact that barbiturates are very hydrophilic ("water-loving") substances, which is illustrated by their relatively low n-octanol/water partition coefficients (log Kow <1.5). Barbiturates appearantly are also poorly removed by treatment steps not involving sorption. As shown in Table 2.1, there are six other DOAs with log Kow ≤1.5, of which codeine is the only one that is also detected at river water intake points. However, unlike barbiturates codeine is not present in raw water and finished drinking water. Also other factors or properties of these substance that determine removal in drinking water treatment are important. However these were not considered in this screening monitoring program.

Pentobarbital and barbital were detected more frequently in raw water and finished drinking water that is produced from bank filtrate than in raw water and finished drinking water that is produced from surface water. This might be related to the greater share of groundwater in bank filtrate. Surface waters where barbital was present ≥LOQ are the Drentsche Aa and the Bethune polder, both areas where upward seepage of groundwater (exfiltration) occurs (see also Figure 3.6). This groundwater is older than the surface waters of the Rhine and Meuse, where barbital was not present ≥LOQ. This older groundwater might be the reason why barbital, a tranquilizer that is no longer available as a prescription drug, is still detected. Although the source of barbital at these sampling locations is not known yet, earlier research showed that dumping sites can be a possible source of barbiturates in groundwater (Eckel et al., 1993; Holm et al., 1995).

Drinking water production sites using surface water (direct treatment)

Figures 3.2 to 3.5 show the results for the individual drinking water production sites that produce drinking water from surface water using reservoirs where degradation or sorption can take place followed by direct treatment. It has to be stressed that these figures are based on only one sampling point in time, the results should therefore be regarded as indicative. At Andijk, IJsselmeer lake water is used for drinking water production. At this site UV-radiation combined with hydrogen-peroxide and activated carbon filtration is employed. The low concentrations of cocaine and its major metabolite benzoylecgonine that are present in IJsselmeer lake water, are not found in the raw water. Phenobarbital, oxazepam and temazepam are detected in the raw, but not in the finished drinking water. The results at Berenplaat (Figure 3.3) and Kralingen (Figure 3.4) show a comparable pattern. At these drinking water production sites, surface water from the river Meuse (Keizersveer) is used as source water after storage in the Biesbosch reservoirs. In the last of the 3-reservoir cascade this water is softened. Afterwards, it is transported to the drinking water production sites employing coagulation/flocculation, sludge blanket clarifiers, double layer filtration and UV-radiation (Berenplaat) or coagulation/flocculation, floc separation and ozonation (Kralingen), followed by double layer filtration and activated carbon filtration. In the raw water of Kralingen a small amount of benzoylecgonine was detected, but not in the finished drinking water.

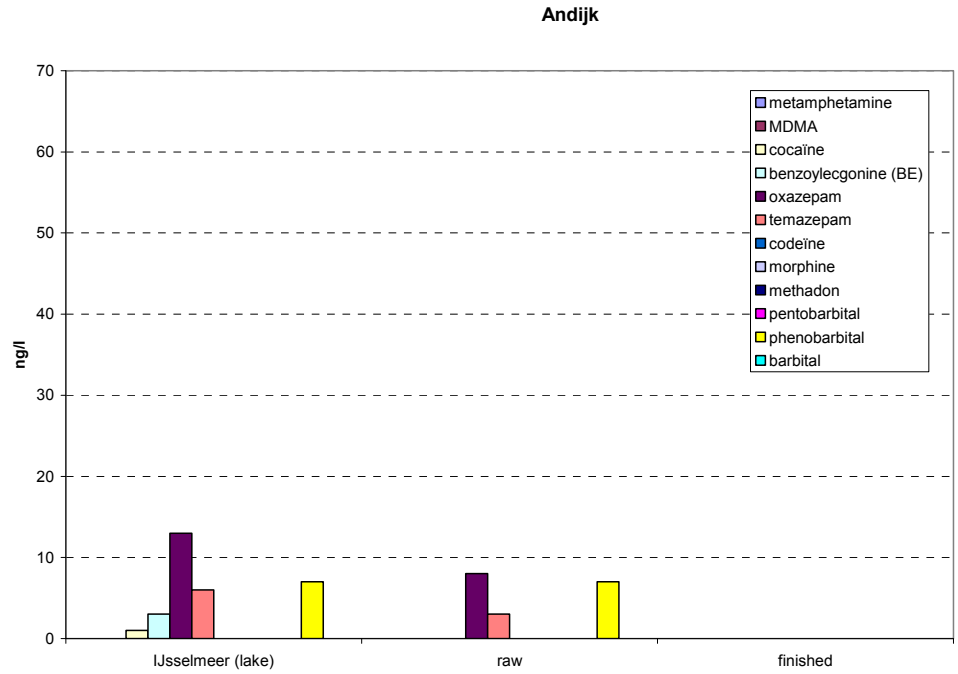

Figure 3.2. Monitoring results DOA for drinking water production site Andijk (PWN)

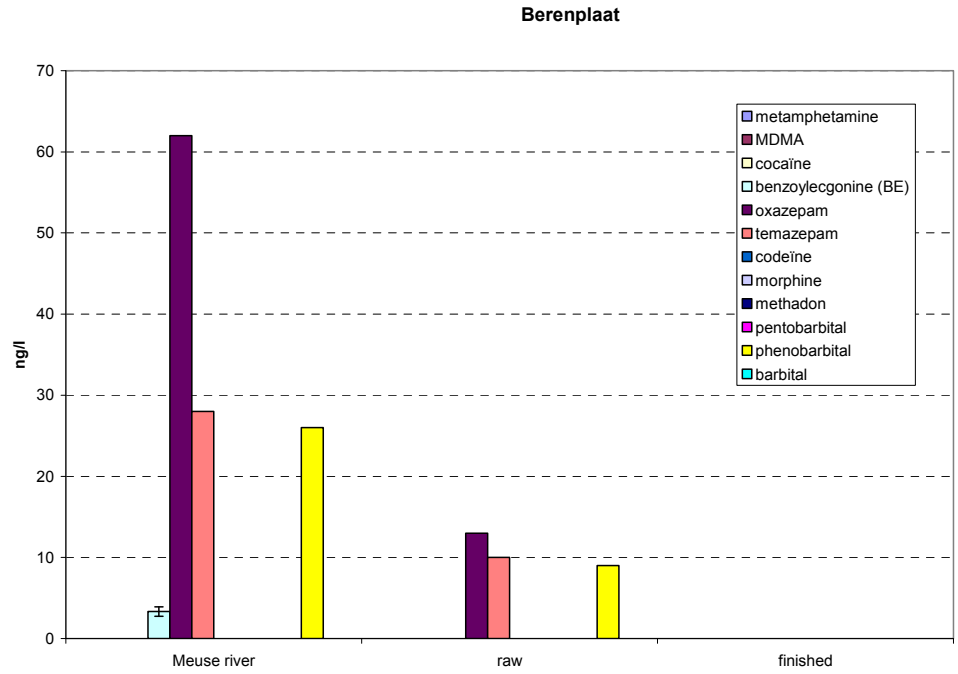

Figure 3.3. Monitoring results DOA for drinking water production site Berenplaat (Evides).Benzoylecgonine was detected by more than one laboratory, therefore standard deviation is presented.

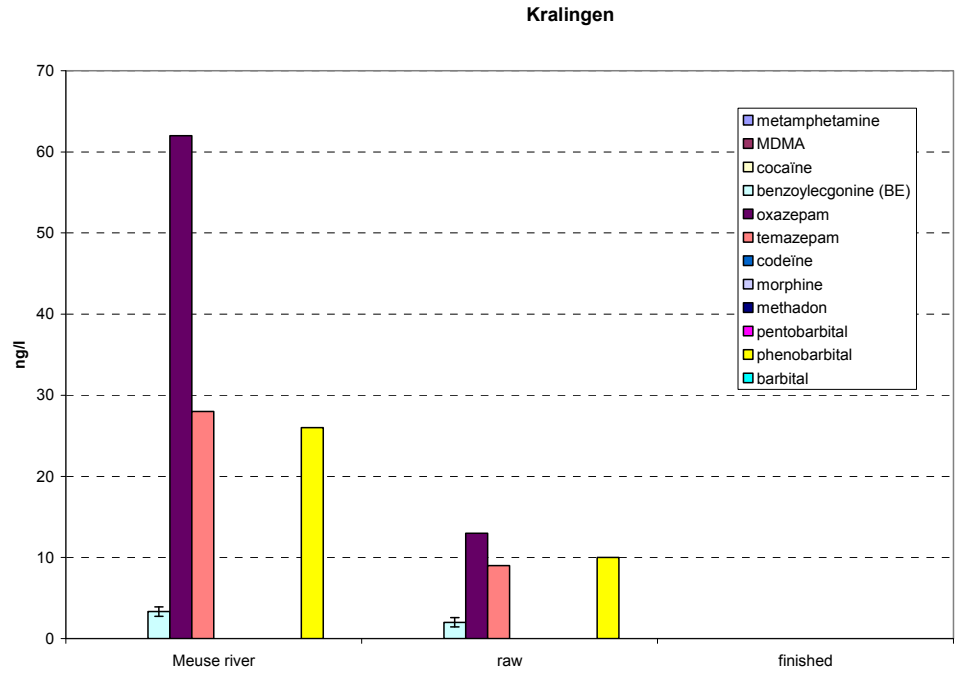

Figure 3.4. Monitoring results DOA for drinking water production site Kralingen (Evides) Benzoylecgonine was detected by more than one laboratory, therefore standard deviation is presented.

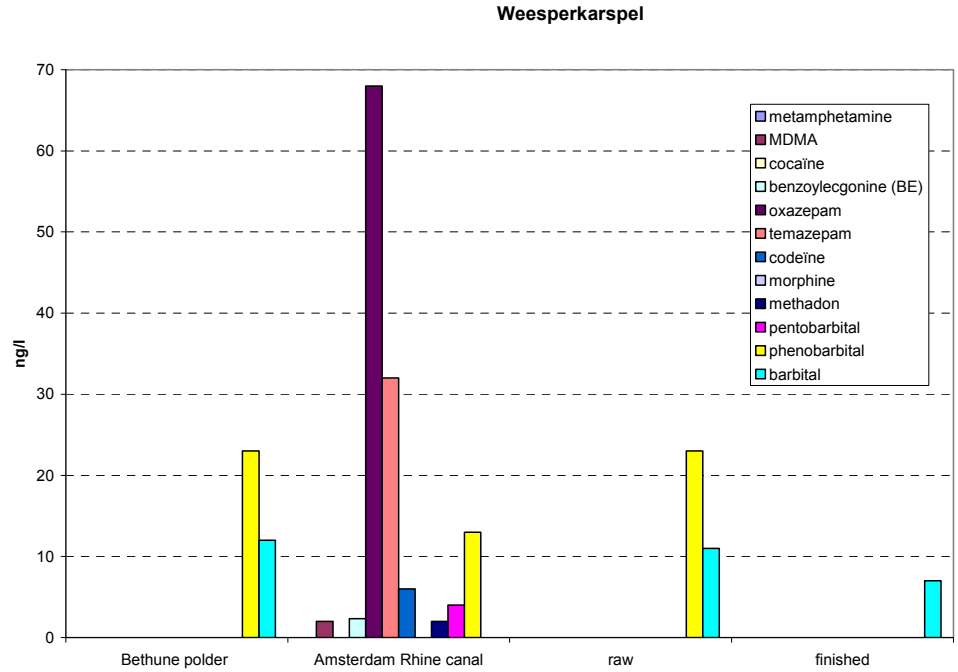

Figure 3.5. Monitoring results DOA for drinking water production site Weesperkarspel (Waternet)

At Weesperkarspel, water from the Bethune polder, an area where upward seepage of groundwater (exfiltration) occurs, is abstracted for drinking water production. Before water is transported to the storage reservoir, it has undergone coagulation. In summer periods, water from the Amsterdam Rhine canal can also be used but this was not the case in 2009. The detected DOA in the raw water and finished drinking water (phenobarbital and barbital) show a comparable pattern with the Bethune polder water and not with the Amsterdam Rhine canal water, where eight different DOA were detected (MDMA, BE, oxazepam, temazepam, codeine, methadone, pentobarbital and phenobarbital). The rapid sand filtration at Loenderveen and ozonation and softening, biologically activated carbon filtration and slow sand filtration employed at Weesperkarspel do not completely remove all barbiturates: although phenobarbital is removed, barbital is still present in the finished drinking water.

Barbital, a tranquilizer that is no longer available as a prescription drug, was the only compound that was detected at the drinking water production site De Punt (Groningen), which uses surface water from the river Drentsche Aa as source water. This compound was observed to be present in the river Drentsche Aa (7 ng/L) and in the raw water (8 ng/L). In the finished drinking water barbital was detected but in a concentration too low to quantify (<LOQ but >LOD). The activated carbon filtration that is performed apparently does not completely remove this compound[2].

Drinking water production sites using surface water and soil aquifer recharge

Figures 3.6 to 3.10 show the results for the drinking water production sites that produce drinking water from surface water using soil aquifer recharge. It has to be stressed that these figures are based on only one sampling point in time, the results should therefore be regarded as indicative. Except for the production site of Heel, where water from the Lateraalkanaal (river Meuse) is temporarily stored in a reservoir then bank filtrated and finally re-abstracted, the infiltration areas involved are located along the coastline (dunes). The pretreated river water is transported to these dune areas, where it is infiltrated after pre-treatment and re-abstracted. After subsoil passage, the re-abstracted water is treated mostly by ozone (except at Ouddorp and Scheveningen), followed by activated carbon.

When comparing the monitoring results of the raw water and finished drinking water, the only compound that was detected in the finished drinking water is phenobarbital at Scheveningen. Apparently, the activated carbon filtration at this site is not effective in completely removing this compound. Besides phenobarbital, all raw waters of Leiduin, Haamstede, Ouddorp and Scheveningen contain detectable levels of the benzodiazepines oxazepam and temazepam, but the benzodiazepines are not present in the finished drinking water.

[2] An additional sampling was performed by order of waterbedrijf Groningen at the drinking water production site De Punt on January 17th, 2011. Water samples from the river Drentsche Aa, raw water and finished drinking were analysed for 6 barbiturates, none of which could be quantified (all concentrations <LOQ). Phenobarbital and pentobarbital were detected in the river Drentsche Aa and in the finished drinking water in a concentration too low to quantify (<LOQ but >LOD)

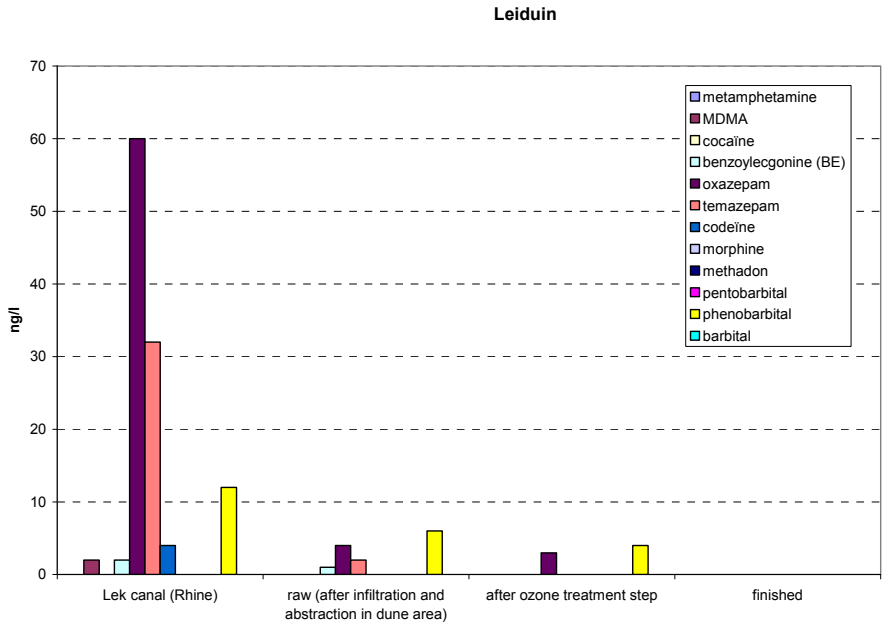

Figure 3.6. Monitoring results DOA for drinking water production site Leiduin (Waternet)

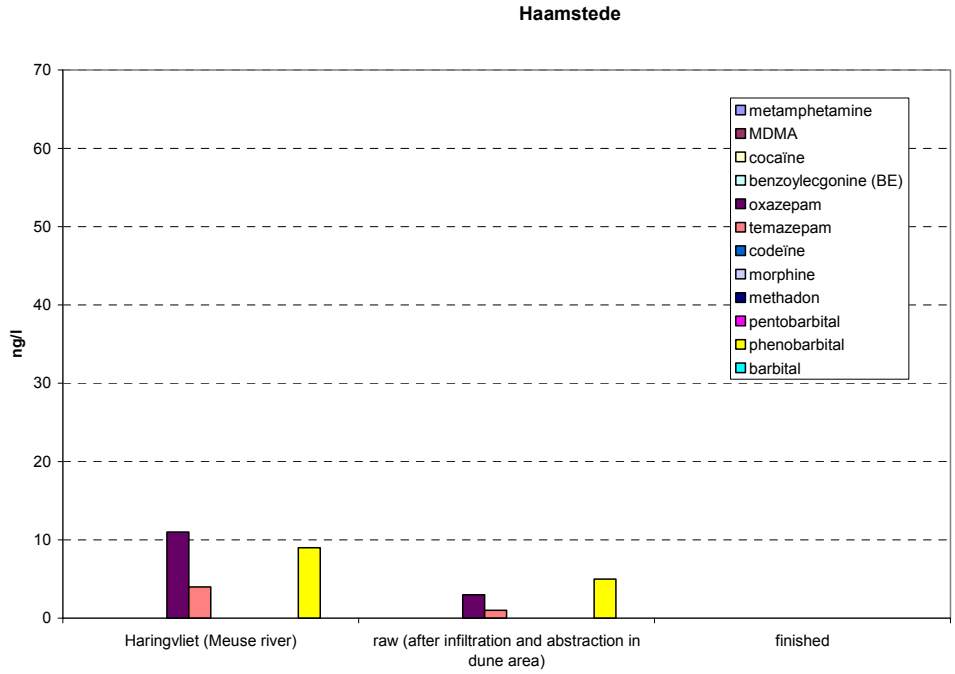

Figure 3.7. Monitoring results DOA for drinking water production site Haamstede (Evides)

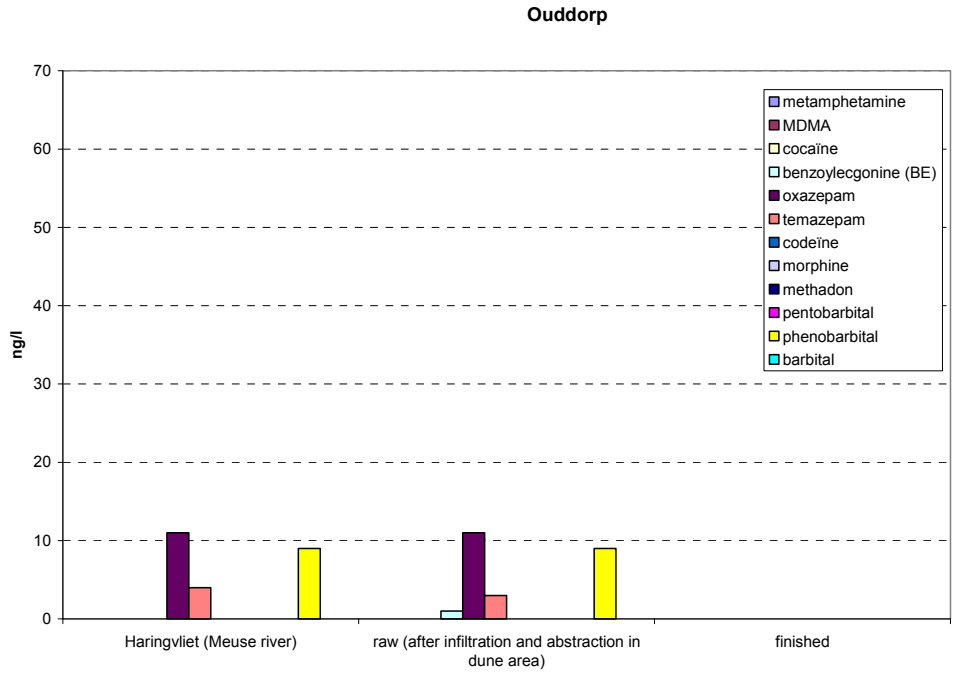

Figure 3.8. Monitoring results DOA for drinking water production site Ouddorp (Evides)

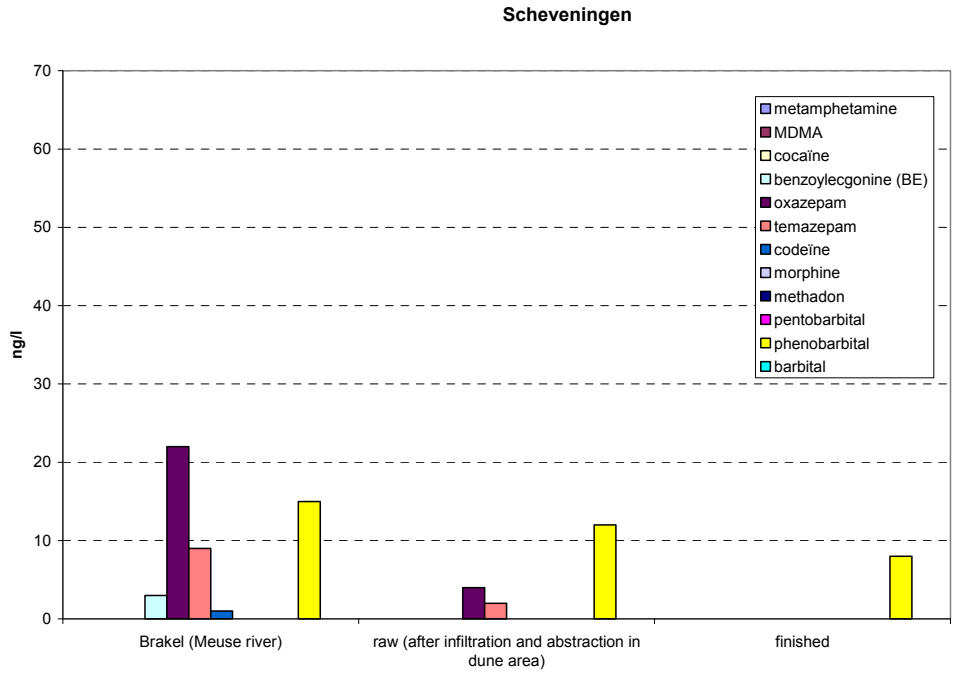

Figure 3.9. Monitoring results DOA for drinking water production site Scheveningen (Dunea)

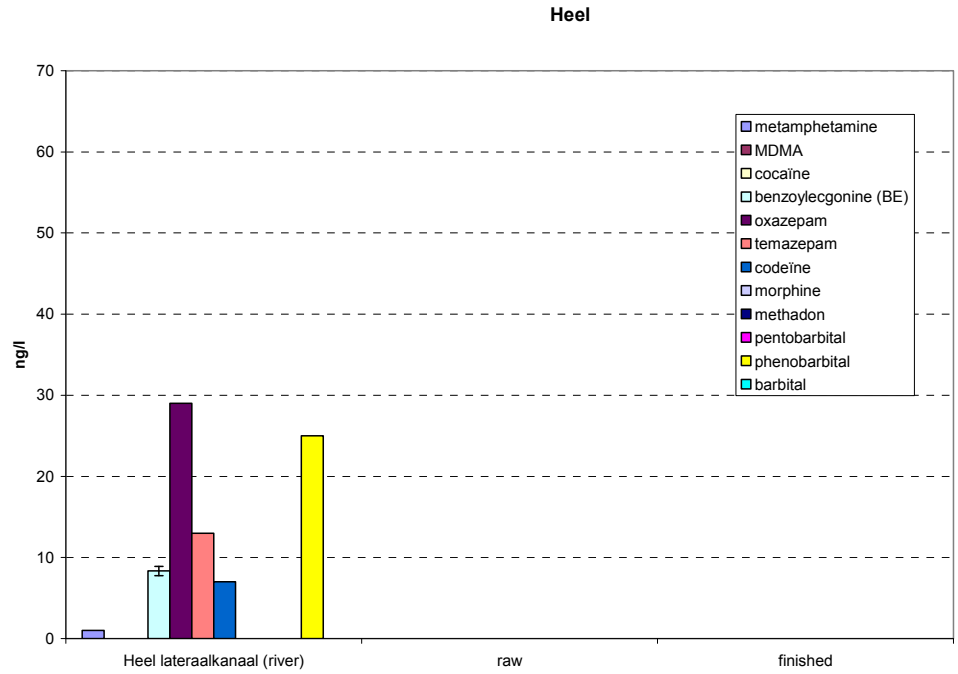

Figure 3.10. Monitoring results DOA for drinking water production site Heel (WML) Benzoylecgonine was detected by more than one laboratory, therefore standard deviation is presented.

At the drinking water production site of Heel, six compounds were observed to be present in the surface water (methamphetamine, benzoylecgonine, oxazepam, temazepam, codeine and phenobarbital) but these were neither detected in the raw water nor the finished drinking water.

Drinking water production sites using bank filtrate

Figure 3.11 shows the barbiturates that were detected at the six production sites were drinking water is produced from bank filtrate (excluding the drinking water production site Roosteren, where no DOAs were present ≥ LOQ (only phenobarbital < LOQ in raw water). It has to be stressed that these figures are based on only one sampling point in time, the results should therefore be regarded as indicative. Out of the total number of 35 DOA and metabolites analysed, only four compounds were detected in the water that is produced from bank filtrate: benzoylecgonine (detected in one raw water sample of Nieuw Lekkerland) and the three barbiturates pentobarbital, phenobarbital and barbital. The three barbiturates were all found to be present in five raw waters and three finished drinking water samples. As shown in Figure 3.11, the concentrations of the barbiturates are sometimes lower or absent in the finished drinking water (Engelse werk, Ridderkerk, Lekkerkerk) but at other production sites the levels were similar or even higher than those in the raw water (notably pentobarbital at Nijmegen, Hendrik-Ido Ambacht, Nieuw-Lekkerland). All of these drinking water production sites use activated carbon in the treatment, mostly in combination with UV-radiation. This treatment is apparently not capable of completely removing the barbiturates.

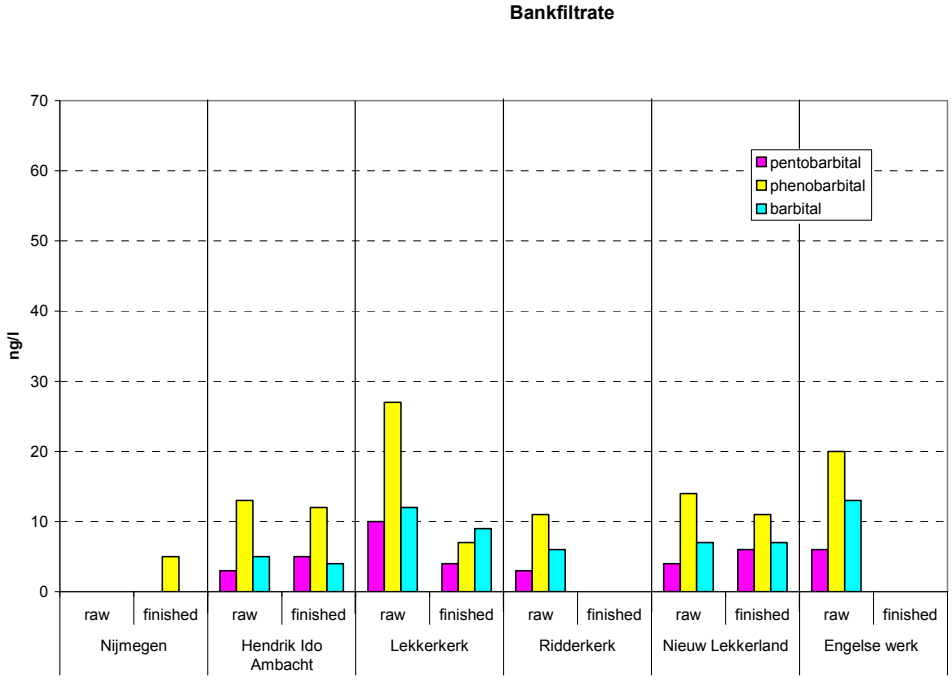

Figure 3.11. Monitoring results DOA for drinking water produced from bank filtrate

3.2 Wastewater

The complete monitoring results from the four different laboratories taking part in the analysis of the wastewater influents and effluents are shown in Appendix F. Table 3.2 presents an overview of those compounds that were present ≥ LOQ. KWR is the only laboratory for which monitoring results are also presented if <LOQ but >LOD. These results were not quantified because the uncertainty involved was considered too big, but qualitatively presented. KWR did not quantify cocaine concentrations in wastewater because of problems with matrix suppression.

Out of the total number of 37 DOA and metabolites analysed, 18 compounds were detected in STP influents and 25 compounds in STP effluent samples. The relatively high standard deviations illustrate that there is considerable variation in detected concentrations at the eight STPs. In the STP influent, compounds were present from the chemical groups amphetamines, barbiturates, benzodiazepines, cannabinoids, cocainics and opiates (Table 2.1). From the group 'others' no compounds were observed above detection limits. Most compounds detected in the STP influent were also detected in the STP effluent, except for the cannabinoid THC-COOH and a metabolite of cocaine (cocaethylene). These compounds might be removed during STP treatment, although firm conclusions about removal efficiency of the STPs can not be drawn based on this research, since STP influent and effluent were sampled on the same day, without accounting for lag-time.

In the STP effluents, the number of different members detected from all DOA groups was larger than in influents except for the cannabinoids, which were not detected in effluents. The mostly somewhat higher LOQs of the influent samples

compared to the effluent samples can only partly explain for this, since often the detected concentrations in de effluent samples are above the LOQ of the influent samples. Barbital, pentobarbital, diazepam, nordazepam, ketamine, methacathinone and ritalin were not detected in influents whereas they were observed in effluents. Concentrations in the STP effluent are mostly lower than in the STP influent, especially for the cannabionoids and the cocainics, suggesting degradation or sorption of these compounds and metabolites in STPs. This is not the case for MDMA (ecstasy) and temazepam, which show higher concentrations in STP effluents and phenobarbital, oxazepam, methadone, EDDP and 6-MAM, which show comparable concentrations in STP influents and effluents.

Deconjugation of conjugates within the STP has been reported as an explanation of higher concentrations of opiates which are excreted in urine mainly as glucuronide metabolites, in effluent compared to influent water (Bones et al., 2007; Rosa Boleda et al., 2007; Kvanli et al., 2008). However, since lag-time was not accounted for in this research (sampling of both the influent and effluent took place on the same day), these differences could also have been caused by different STP influent concentrations one or a few days earlier. Matrix suppression of the influent might also be an important factor. A conclusion that can be drawn however, is that 25 out of 37 DOA were able to pass the STP .

Table 3.2. Average concentrations of DOA detected ≥ LOQ in STP influents and effluents

Chemical class	Compound	STP influent (n=8)			STP effluent (n=8)		
		avg conc. (ng/L)	SD	n ≥ LOQ	avg conc. (ng/L)	SD	n ≥ LOQ
Amphetamines	amphetamine	334	179	8 (100%)	15		1 (13%)
	metamphetamine	151	180	2 (25%)	37	20	4 (50%)
	MDA				22		1 (13%)
	MDMA	109	51	8 (100%)	126	174	8 (100%)
Barbiturates	pentobarbital				13	9	4 (50%)
	phenobarbital	98	44	6 (75%)*a	96	54	8 (100%)
	barbital				15		1 (13%)
Benzodiazepins	diazepam				4	1	5 (63%)
	nordazepam				19	7	5 (63%)
	oxazepam	1167	445	8 (100%)	1122	375	8 (100%)
	temazepam	427	179	8 (100%)	568	198	8 (100%)
Cannabinoids	THC-COOH	424	137	7 (88%)*a			
Cocaïnics	cocaïne	438	245	8 (100%)	4	3	6 (75%)
	benzoylecgonine (BE)	1703	870	8 (100%)	26	25	8 (100%)
	cocaethylene (CE)	27	19	7 (88%)			
	norbenzoylecgonine	36	16	6 (75%)	4	1	4 (50%)
	norcocaine	20	10	6 (75%)	4		1 (13%)
	ecgonine methylester	207	97	4 (100%)*b	41	2	3 (75%)*b
Opiates	fentanyl				8		1 (13%)
	6-MAM	3		1 (13%)	5	2	2 (25%)
	morphine	665	418	8 (100%)	31	22	7 (88%)
	codeïne	580	230	8 (100%)	192	88	8 (100%)
	methadon	37	20	4 (50%)	29	19	8 (100%)
	EDDP	84	41	4 (100%)*b	73	43	4 (100%)*b
Others	ketamine				16	12	6 (75%)
	methacathinone				4		1 (13%)
	ritalin / methylphenidate				5	3	6 (75%)

*a detected in one other STP influent sample but not quantified because below LOQ

*b only four STPs (Utrecht, Apeldoorn, Amsterdam West and Eindhoven) analysed by UA

3.3 Estimated loads of DOA based on monitoring data

3.3.1 Loads through the Rhine and Meuse rivers

The loads of DOA transported by rivers are calculated by multiplying the concentrations measured and the flow rate at the sample location on the sampling date. Flow rates on the sampling dates were obtained from Rijkswaterstaat – waterbase. Figure 3.12 shows the loads calculated for the rivers Rhine and Meuse. For comparison, the load for oxazepam at Lobith is comparable or even higher than the load of widely used pharmaceuticals, such as various antibiotics, beta blockers, lipid regulators or anti-inflammatory pharmaceuticals (Ter Laak et al., 2010). The concentrations in the river Meuse were higher than in the river Rhine, as shown in Figure 3.13. However, the loads in the river Rhine are higher because of the much higher flow rate.

The loads are also calculated at two locations downstream: Keizersveer (river Meuse) and Maassluis (river Rhine). As shown in Figure 3.13, the loads increase downstream for the five compounds presented, except for codeine and benzoylecgonine in the river Meuse. These numbers are indicative because they are based on only one sampling date and further research with more monitoring data is necessary on this topic. However, increasing loads of the rivers Rhine and Meuse when flowing through the Netherlands are plausible because the prescription drugs phenobarbital, oxazepam, temazepam and codeine are consumed in the Netherlands in quantities of approximately 200 - 1500 kg per year, according to sales data from the Foundation for Pharmaceutical Statistics in the Netherlands (SFK, 2007). Residues of these compounds can reach the Dutch surface waters through STP wastewater discharges since they are poorly removed in STPs. For the river Meuse there can also be a contribution from Belgian and German rivers that discharge their waters into the river Meuse downstream from Eijsden.

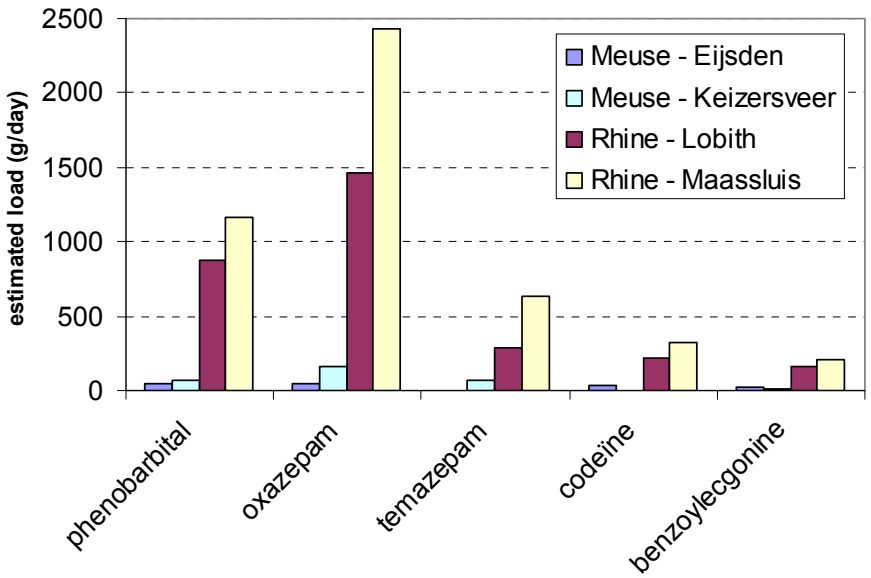

Figure 3.12. Estimated loads (g/day) of DOA based on monitoring data and river flow rates on one sampling date in October 2009

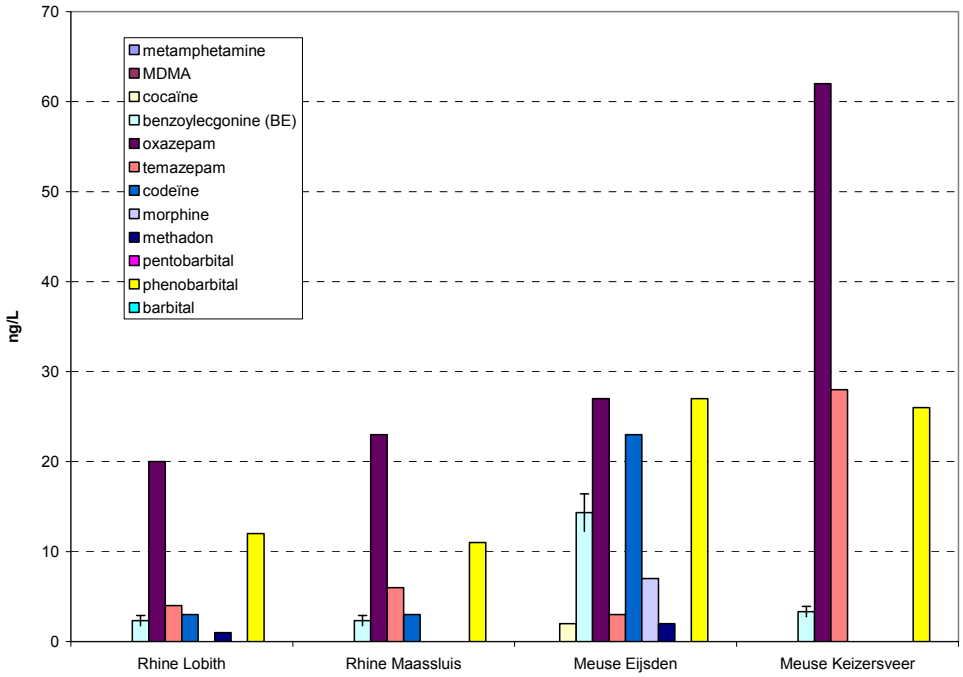

Figure 3.13. Monitoring results for DOA at the Dutch entrance points (Rhine Lobith and Meuse Eijsden) and two sampling locations downstream

3.3.2 Loads through STPs

Figure 3.14 shows the calculated loads discharged from the eight Dutch STP effluents that were monitored. Amsterdam West is the STP with the highest Inhabitant Equivalent (I.E.) and Culemborg the lowest. This generally corresponds to the loads of DOA discharged from these STPs, which are highest at Amsterdam West and lowest at Culemborg, although there are exceptions. The influence of STP size can be eliminated by presenting the results per I.E. as is shown for cocaine in STP influents in Figure 3.16.

For phenobarbital, a compound that is clearly difficult to remove during treatment, the STP loads are compared with loads calculated with consumption data from the Foundation for Pharmaceutical Statistics in the Netherlands (SFK, 2007). After consumption, 25% of the consumed amount of phenobarbital is excreted by the human body unchanged in urine (KNMP, 2007). Phenobarbital is also excreted as a metabolite of primidone: 15–25% of the consumed amount according to KNMP (2007). Taking into account these factors, the expected loads of phenobarbital towards the 8 STPs are calculated based on the average daily consumption in the Netherlands and the number of I.E. of the STP. Figure 3.15 shows the results of this calculation and a comparison with the loads of phenobarbital through STP influents and effluents based on the monitoring data. With the exception of the STP Den Bosch and Amsterdam West, the estimated loads based on consumption, are within a factor of two of the estimated loads based on monitoring data and flow rates. This is considered acceptable considering the data limitations (only one sampling date, average consumption data for the Netherlands in 2007) and it illustrates that besides possible 'abuse', prescription use is probably an important source for phenobarbital. However,

further research with additional and more frequent monitoring data is necessary on this topic. This can shed more light on sources of this compound and possible adaptation measures in preventing this compound from reaching Dutch drinking water.

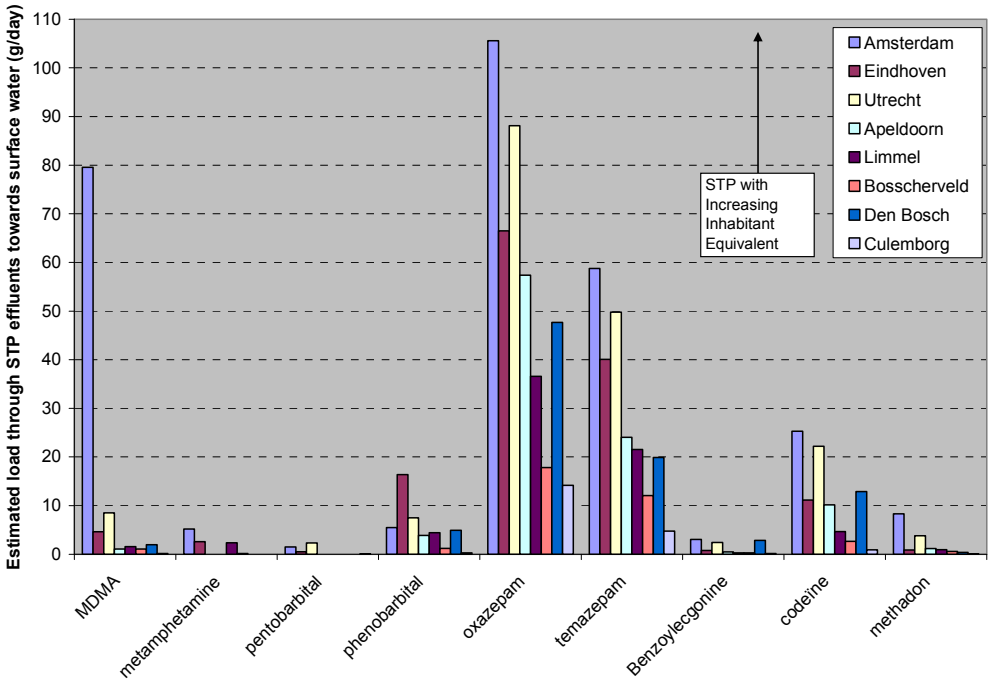

Figure 3.14. Estimated loads (g/day) of DOA based on monitoring data and STP flow rates in October 2009

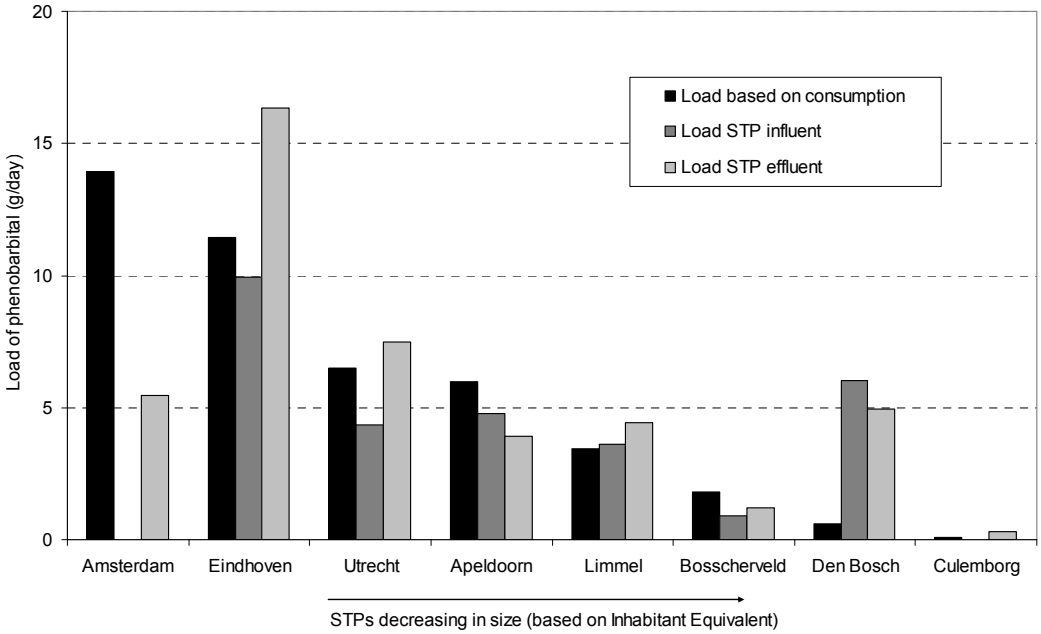

Figure 3.15. Comparison between loads of phenobarbital that are calculated based on I.E. and average consumption in the Netherlands (SFK, 2007) and loads through STP influents and effluents based on monitoring data in October 2009

3.3.3 Estimated cocaine consumption of the population

Based on the concentrations of benzoylecgonine measured, the equivalent amount of cocaine can be back-calculated as cocaine consumption per I.E. of the STP, according to the method presented by Zuccato et al (2005). To that end, the actual calculated population equivalents served on that day and the 24-hour flow are used. The method is explained in Appendix G. Figure 3.16 shows both the total load of pure cocaine towards the STP (influent) and the estimated consumption of cocaine per 1000 inhabitants of the 8 STPs on the sampling date (between October 4 and November 11, 2009). The results show that the total load of cocaine (grey bars) generally decreases with decreasing STP size: the total load is highest at Amsterdam West and lowest at Culemborg, although there are exceptions. This is not the case for the estimated cocaine consumption per 1000 inhabitants, which is independent from the size of the STP. Cocaine consumption per 1000 inhabitants is clearly lower in the towns of Apeldoorn and Culemborg than in the cities of Amsterdam, Utrecht, Maastricht (STP Limmel and Bosscherveld), Eindhoven and Den Bosch. Amsterdam clearly shows the highest consumption. The estimated cocaine consumption of these Dutch cities on weekend days is within the range of cocaine consumption as estimated by Nuijs et al. (2009b) for 41 Belgian cities. This topic will be further described using STP week-trend sampling data in a report that is being prepared by KWR (Bijlsma et al, in prep).

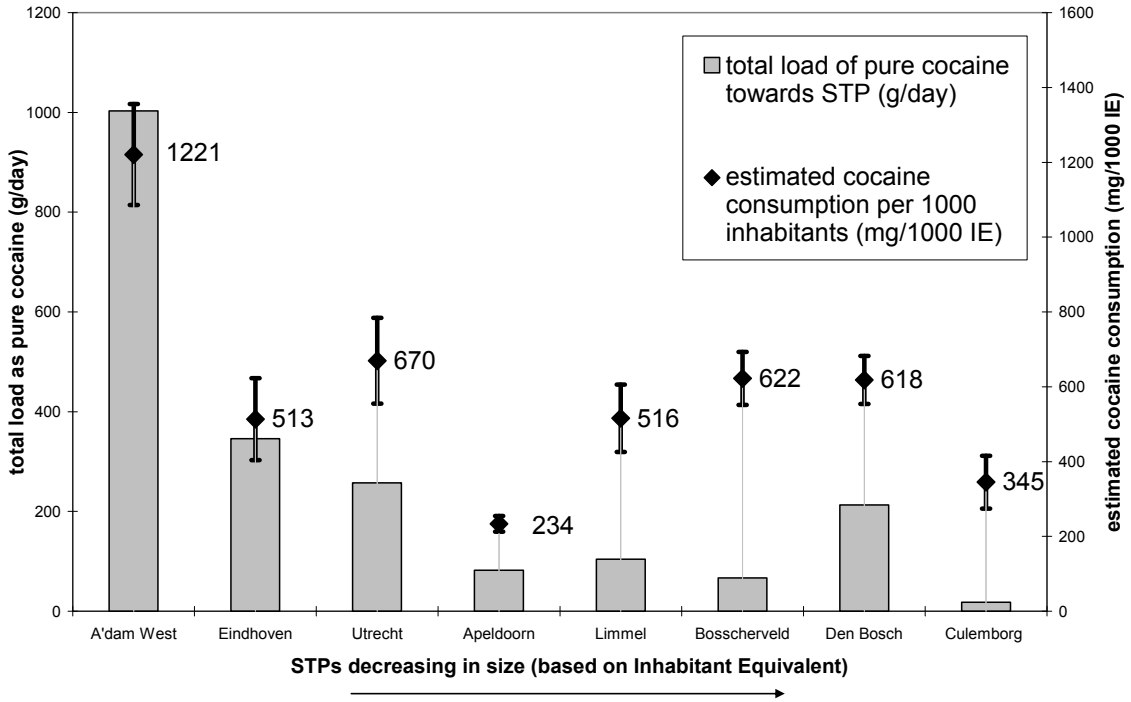

Figure 3.16. Estimated total cocaine loads per day from STP influents and estimated consumption per 1000 inhabitants

3.4 Comparing results of the three laboratories

From the total of 37 DOA and metabolites that were analysed in this monitoring campaign, 12 compounds were analysed by two or more laboratories. In order to compare the monitoring results of all laboratories, the monitoring data that

were ≥ LOQ at all labs were selected. This resulted in three compounds (benzoylecgonine, amphetamine and MDMA) and 16 samples that could be compared (6 surface water, 5 STP influent and 5 STP effluent). Table 3.4 shows the average concentrations with relative standard deviation and for each laboratory the relative deviation from the average concentration. The table shows that KWR for all but one sample presented here, detected 4% to 59% higher concentrations compared with the calculated average concentrations. The differences between the laboratories of UJI, RIVM and UA were smaller. They detected mostly lower concentrations; +6 to –23% (UJI), +13 to –29% (RIVM) and –2 to –28% (UA). Differences between the laboratories are highest for two STP effluent samples on benzoylecgonine: +59% (KWR) versus –28% (UA) and +51% (KWR) versus –29% (RIVM). The deviation in the STPs can be attributed to a combination of matrix suppression and the concentration factor. The differences are considered acceptable.

Table 3.4. Deviation per laboratory (%) from the average concentration of all laboratories

Water type	Compound	Avg conc (ng/l)	Rel.st.dev (%)	Rel. deviation from average concentration per lab (%)			
				KWR	UJI	RIVM	UA
influent	Benzoylecgonine	1733	16	29	-22	-4	-3
influent	Benzoylecgonine	570	8	-3	-7	13	-3
influent	Benzoylecgonine	1193	17	23	-1	-5	-17
influent	Benzoylecgonine	2907	10	12	6	-5	-13
effluent	Benzoylecgonine	21	38	59	-23	-8	-28
effluent	Benzoylecgonine	26	38	51	-2	-29	-21
effluent	MDMA	54	26	33	-20	9	-22
effluent	MDMA	92	24	35	-9	-4	-22
effluent	MDMA	537	20	28	-8	-1	-20
influent	amphetamine	107	8	4	-11	9	-2
surface water	Benzoylecgonine	14	15	5	-16	12	-
surface water	Benzoylecgonine	2.3	0	29	-14	-14	-
surface water	Benzoylecgonine	2.3	26	29	-14	-14	-
surface water	Benzoylecgonine	2.3	26	29	-14	-14	-
surface water	Benzoylecgonine	3.3	18	20	-10	-10	-
surface water	Benzoylecgonine	8.3	7	8	-4	-4	-

3.5 Comparing Dutch monitoring results with other countries

Average concentrations of some drugs of abuse detected in Dutch urban wastewaters are compared with concentration levels in wastewaters from other European countries (see Figure 3.17 (STP influent) and Figure 3.18 (STP effluent)). However, precaution on the interpretation of the data is required, as a one-to-one comparison is difficult to make. For a correct comparison of the data, various factors such as weather conditions at time of sampling; treatment, capacity and lag-times of the STPs, etc, need to be taken into account. This would implicate a much more extensive study. Therefore, illustrated figures are only presented to give an indication of the range of DOA concentrations detected in STPs in four Western-European countries. Averages for Spain are calculated from data from Postigo et al. (2008), Huerta-Fontela et al. (2007) and Bijlsma et al. (2009), excluding the monitoring data that were acquired during a festival. Averages for the UK and Ireland are calculated from data from Kasprzyk-Hondern et al. (2008) and Bones et al. (2007). Averages for Italy are calculated from data from Castiglioni et al. (2006).

As can be observed from Figure 3.17 and 3.18, concentrations in the Netherlands are within an order of magnitude difference of the concentrations in the countries Spain, UK and Italy. Exceptions are the relatively high concentrations reported in the UK for amphetamine, cocaine, benzoylecgonine and morphine in effluent wastewater. Concentrations of THC-COOH and morphine in Dutch influent seem somewhat higher and concentrations of cocaine and benzoylecgonine in Dutch effluents seem somewhat lower than those observed in the other countries. From the compounds presented, cocaine and its human metabolite benzoylecgonine were most abundantly detected in wastewater influents and effluents, with concentrations in influents of between approximately 500 and 2000 ng/L, respectively. Amphetamine, methamphetamine, amphetamine-type stimulants (MDMA, MDMA, MDEA), THC-COOH and opiates (methadone and morphine) were present in wastewater influents at lower concentration levels in the range of 37–665 ng/l. An exception is the relatively high concentration for amphetamine reported in the UK (2753 ng/L) Concentrations of drugs and metabolites were lower in effluents than influents, suggesting degradation or sorption of these substances and metabolites in wastewater treatment plants. This was confirmed in other studies in treatment plants in other European countries (Boleda et al., 2007; Huerta-Fontela et al., 2007; Postigo et al., 2008; Bijlsma et al., 2009). However, significant amounts of illicit drugs and metabolites were still present in effluents and consequently will end up in the receiving water bodies, i.e., surface/river water (Boleda et al., 2007; Huerta-Fontela et al., 2007; Vanderford and Snyder., 2006; Hummel at al., 2006).

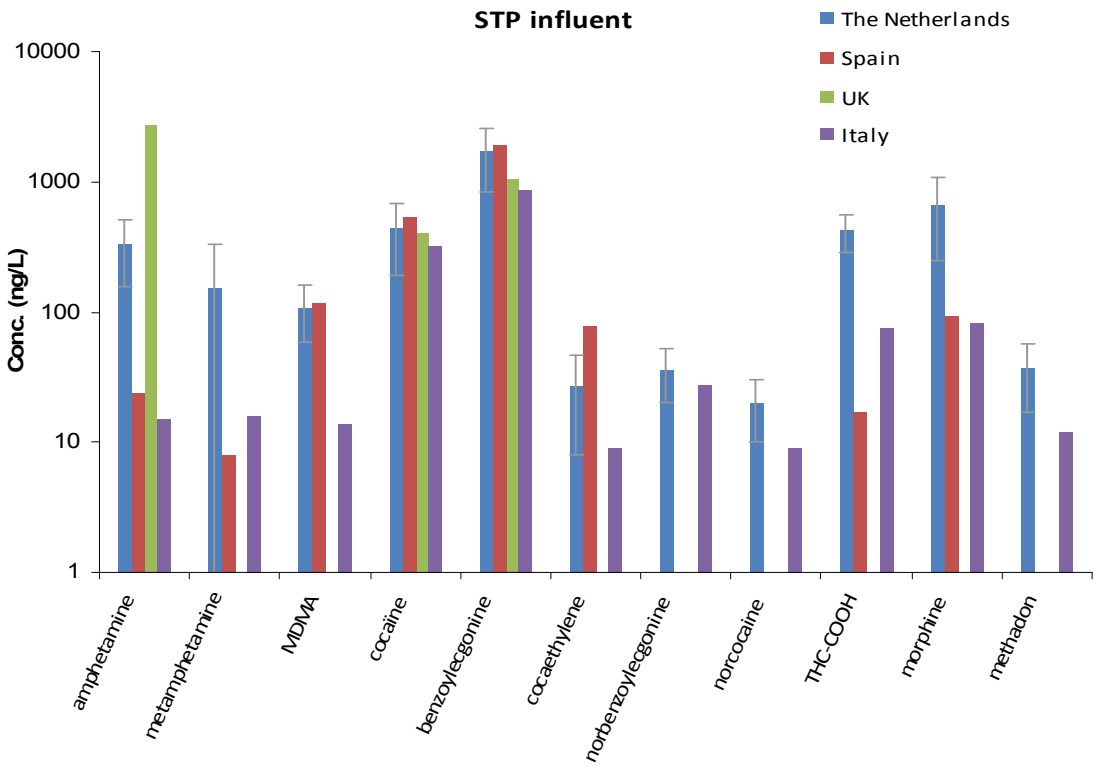

Figure 3.17. Comparison of average concentrations from Dutch STP influents with three other European countries

An illustrative comparison between concentrations of drugs of abuse in Dutch surface waters and in other European countries has not been made thus far. In one study, the opioids, morphine, codeine and its metabolite hydrocodeine and two tranquilizers oxazepam and temazepam were detected in river water at concentration levels between 80 and 400 ng/L (Hummel at al., 2006). In another study, concentration levels detected in surface waters in Spain were between 6 and 26 ng/L for codeine, norcodeine, morphine and methadone and between 14 ng/L and 34 ng/L for delta-9-tetrahydrocannabinol (delta-9-THC) and its human metabolite THC-COOH, respectively (Boleda et al., 2007). Our data for surface waters (Table 3.1) which mostly cover the rivers Rhine and Meuse, demonstrated similar concentrations for opiates and lower concentrations for oxazepam (6–68 ng/L) and temazepam (3–32 ng/L). THC-COOH was not detected. Zuccato et al. (2008b) reported concentrations of cocaine and benzoylecgonine in Italian surface waters up to 44 ng/L and 183 ng/L, respectively. Huerta-Fontela (2008) report the presence of cocaine, benzoylecgonine, amphetamine, methamphetamine, MDMA(ecstasy) and MDA in Spanish surface waters at concentrations ranging from 4 to 350 ng/L. From these compounds, methamphetamine, MDMA, cocaine and benzoylecgonine were detected in Dutch surface waters of the Rhine and Meuse in lower concentrations: up to 16 ng/L.

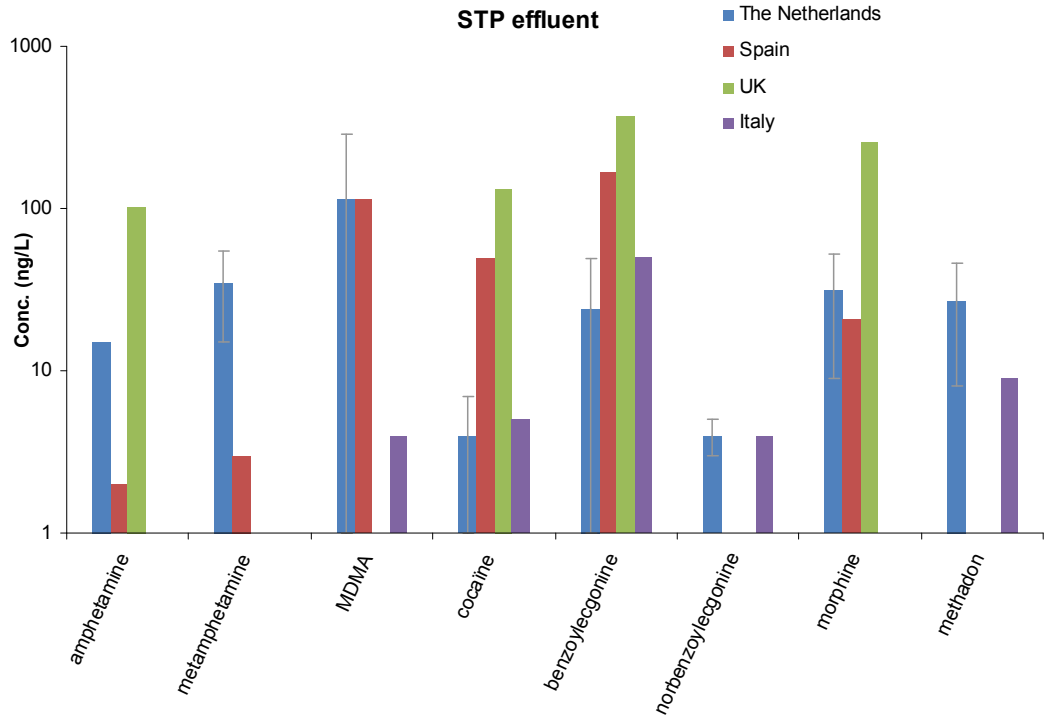

Figure 3.18. Comparison of average concentrations from Dutch urban wastewater effluents with three other European countries

3.6 Provisional drinking water limits for DOA

The concentrations of the DOA detected in drinking water are below the general signal value of 1 µg/L which is specified for organic compounds of anthropogenic

origin in the Dutch Drinking water act. For individual DOA, no statutory drinking water standards are available. Therefore, for the twelve DOA that were detected in surface waters, provisional drinking water limits were determined. A limited literature search was carried out to obtain data on the toxicological and pharmacological action of the drugs. For all drugs, pharmacological action appeared a more sensitive criterion than toxicity. Because no ADI (Acceptable or tolerable Daily Intake) or MRL (Maximum Residue Limit) were available, provisional drinking water limits were determined from the lowest pharmacologically effective dose for the different drugs by applying a safety factor of 100 and using an assumed average body weight of 60 kg and a consumption of 2 L of drinking water per day. The method of limit derivation is further described in Appendix H.

Although it is known that some drugs interact at pharmacologically effective doses, no information was available on their possible interaction at the level of the proposed drinking water limits. Therefore, no attempt was made to determine drinking water limits for combinations of drugs. Only for drugs belonging to the same chemical group that are known to have the same mechanism of action a drinking water limit was derived for the whole group.

For pentobarbital, phenobarbital and barbital, a common provisional drinking water limit is derived as these drugs act by a common mechanism. When these compounds occur together in drinking water, the sum of their concentrations should not exceed 50 µg/L (Table 3.5). For temazepam and oxazepam a common provisional drinking water limit is also derived based on a common mechanism of action. When these compounds occur together in drinking-water, the sum should not exceed 8 µg/L.

Table 3.5 shows a comparison of the provisional drinking water limits with the maximum concentrations detected in STP effluent, surface water, raw water and finished drinking water, respectively. The table shows that for the three barbiturates that are detected in finished drinking water, the provisional drinking water limit is about 1800 times higher than the actual concentrations detected. For the six substances that were detected in raw water (benzoylecgonine, sum oxazepam and temazepam and sum pentobarbital, phenobarbital and barbital), the provisional drinking water limits are between 300 and 7000 times higher than the detected concentrations. These findings are in agreement withc conclusions of Schriks et al. (2009) and Bruce et al. (2010) who performed a toxicological assessment of pharmaceuticals in drinking water. Based on this information, the health risks for humans drinking this water are negligible. However, much less is known about possible long-term (chronic) effects on human health and possible effects of combined exposure to multiple compounds at low concentrations.

For the surface waters of the rivers Rhine and Meuse, the provisional drinking water limits for all substances are more than 1000 times higher than the concentrations detected, except for the sum of oxazepam and temazepam (provisional drinking water limit 80 times higher).

In the STP effluents, the safety margins between provisional drinking water limits and the concentrations detected are smaller. For sum oxazepam and temazepam the provisional drinking water limit is smallest: only three times higher than the maximum concentration detected. For MDMA and codeine the provisional drinking water limit is respectively 70 and 80 times higher than the

concentration detected. For the other substances, the provisional drinking water limit is more than 100 times higher.

Table 3.5. Comparison of provisional drinking water limits[a] with the detected maximum concentrations in STP effluent, surface water, raw water and finished drinking water.

		WWTP effluent		Surface water Rhine / Meuse		Raw water		Finished drinking water	
	Provisional drinking water limit (µg/L)	Max conc (µg/L)	risk ratio *	Max conc (µg/L)	risk ratio *	Max conc (µg/L)	risk ratio *	Max conc (µg/L)	risk ratio *
benzoylecgonine	20	0.089	**225**	0.016	**1250**	0.003	**6667**	-	
cocaïne	20	0.014	**1429**	0.003	**6667**	-		-	
MDMA	50	0.69	**72**	0.002	**25000**	-		-	
metamphetamine	15	0.096	**156**	0.001	**15000**	-		-	
codeïne	30	0.378	**79**	0.023	**1304**	-		-	
morphine	15	0.068	**221**	0.007	**2143**	-		-	
methadon	10	0.057	**175**	0.002	**5000**	-		-	
oxazepam	sum 8	1.746	sum 2.76	0.068	sum 0.1	0.013	sum 0.023	-	
temazepam		1.016	**3**	0.032	**80**	0.01	**348**	-	
pentobarbital		0.025		0.004		0.01		0.006	
phenobarbital	sum 50	0.191	sum 0.23	0.027	sum 0.043	0.027	sum 0,050	0.012	sum 0,027
barbital		0.015	**217**	0.012	**1163**	0.013	**1000**	0.009	**1852**

[a] for derivation, see Appendix H

* risk ratio: ratio of provisional drinking water limit to maximum concentration

4 Conclusions and recommendations

4.1 Conclusions

This first Dutch screening monitoring campaign confirms the presence of DOA and tranquilizers in the Dutch water cycle. A total number of 37 DOA and metabolites was analysed by four laboratories RIVM, KWR Watercycle Research Institute, University Jaume I (Spain) and University of Antwerp (Belgium).

Surface water

In the surface waters of the rivers Rhine and Meuse, 12 DOA were detected in concentrations up to 68 ng/L:

- the amphetamine-type stimulants methamphetamine and MDMA (Ecstasy)
- cocaine and its major metabolite benzoylecgonine
- the opiates codeine, morphine and methadone
- the barbiturates pentobarbital, phenobarbital and barbital
- the benzodiazepines oxazepam and temazepam

Phenobarbital, oxazepam, temazepam and benzoylecgonine were most abundantly present: at > 70% of the total of 14 surface water sampling locations.

Raw water and finished drinking water

In raw water, six DOA were detected at concentrations up to 27 ng/L:

- the barbiturates pentobarbital, phenobarbital and barbital
- the benzodiazepines oxazepam and temazepam
- benzoylecgonine

In finished drinking water, three compounds were detected: the barbiturates pentobarbital, phenobarbital and barbital, at concentrations up to 12 ng/L. Benzoylecgonine, the main metabolite of cocaine, was detected in one finished drinking water sample but at a concentration < LOQ (1 ng/L). From the 17 finished drinking water samples, 6 samples (35%) contained one or more barbiturates ≥ LOQ. When the monitoring results above LOD but below LOQ (2-4 ng/L) are also taken into account, 13 samples (76%) contained one or more barbiturates. Phenobarbital is detected most frequently, followed by barbital and pentobarbital.

Drinking water treatment

The amphetamine-type stimulants, cocainics and opiates that are present at the river water intake points are not present in the raw water. The raw water contains reduced concentrations of oxazepam, temazepam, benzoylecgonine and phenobarbital compared to their concentrations detected at the river water intake points. Apparently, these compounds are to some extent removed during reservoir storage, pre-treatment or soil aquifer recharge that take place between the river water intake point and the raw water sampling location. Benzodiazepines are not detected in the raw water that is produced from bank filtrate: possibly they have been removed during bank filtration.

Barbiturates appear only to get partly removed during drinking water treatment
Pentobarbital and barbital were detected more frequently in raw water and finished drinking water that is produced from bank filtrate than in raw water and finished drinking water that is produced from surface water. The presence of barbital might be related to the greater share of older groundwater in bank filtrate. This might be the reason why barbital, a tranquilizer that has been used as a human medicine since the beginning of the 20th century, is still detected although it is no longer available as a prescription drug.

Urban wastewater

Out of the total number of 37 DOA and tranquilizers analysed, 18 compounds were detected in STP influents and 25 compounds in STP effluent samples. Most compounds detected in the STP influent were also detected in the STP effluent, except for the cannabinoid THC-COOH and a metabolite of cocaine (Cocaethylene). Compounds from all chemical groups except the cannabinoids were present in STP effluents: amphetamines, barbiturates, benzodiazepines, cocainics, opiates and others. Some compounds were found to be absent in influents whereas they were observed in effluents. This can be a result of transformation processes during treatment, for example, de-conjugation of conjugates within the STP. For some compounds the somewhat higher LOQs of the influent samples compared to the effluent samples, can also play a role. Concentrations of most of the DOA and metabolites were lower in effluents than influents, suggesting degradation or sorption of these substances and metabolites in wastewater treatment plants. This is in agreement with findings reported in several studies in treatment plants in other European countries. Exceptions included the benzodiazepines, the barbiturates and ketamine. Concentrations in the Dutch STPs are mostly of the same order of magnitude as those from Spain, UK and Italy, although a comparison could not be made for all compounds. For example, barbiturates have not yet been investigated in other countries.

Loads of DOA through rivers and wastewater

Substantial fractions of the total load of drugs in the Rhine and Meuse rivers enter the Netherlands from abroad. At Lobith, the load for oxazepam is highest and comparable to or even higher than the loads of broadly used pharmaceuticals such as various antibiotics, beta blockers, lipid regulators or anti-inflammatory pharmaceuticals. For some compounds loads seem to increase downstream, which is probably caused by a contribution from STP effluents.

For phenobarbital, the STP loads calculated based on consumption are mostly within a factor 2 of the estimated loads based on monitoring data and flow rates. Although these numbers are indicative, it illustrates that besides possible ‘abuse’, prescription use is probably an important source for this so-called soft drug, which is listed as a List II substance in the Dutch Opium act. Prescription use is also an important source for the benzodiazepins oxazepam and temazepam which were among the top10 of most prescribed pharmaceuticals in the Netherlands in 2007 and 2008.

Monitoring data can also be used to back-calculate consumption. Based on the measured concentrations for benzoylecgonine, cocaine consumption could be estimated for the areas supplying the STPs in eight Dutch cities, showing a variable level of estimated drug consumption. The estimated cocaine

consumption of these Dutch cities is within the range of cocaine consumption for 41 Belgian cities as estimated in other studies.

Comparison with provisional drinking water limits

The concentrations of the DOA detected in drinking water are below the general signal value of 1 µg/L, which is specified for organic compounds of anthropogenic origin in the Dutch Drinking water act. To assess possible risks to human health, provisional toxicological limits for drinking water were derived based on the currently available toxicological knowledge.

For the three barbiturates that are detected in finished drinking water, the provisional drinking water limit is about 1800 times higher than the actual concentrations detected. Based on this information, effects on public health are not expected. However, possible effects of combined exposure to multiple compounds in low concentrations are less clear.

For the substances that are detected in raw water (benzoylecgonine, sum oxazepam and temazepam, and sum pentobarbital, phenobarbital and barbital), the provisional drinking water is between 300 and 7000 times higher than the concentrations detected. For the surface waters of the rivers Rhine and Meuse, the provisional drinking water limits for all substances are more than 1000 times higher than the concentrations detected, except for sum oxazepam and temazepam (provisional drinking water limit 80 times higher).In the STP effluents, the safety margins between the provisional drinking water limits and the concentrations detected are smaller. For sum oxazepam and temazepam the the provisional drinking water limit is smallest: three times higher than the maximum concentration detected. For the other compounds the the provisional drinking water l limit is about 100 – 1500 times higher.

4.2 Recommendations

Although there is no indication of human health risks with respect to the compounds detected in finished drinking water, alertness is required. Ongoing research with respect to possible effects of combined exposure to multiple compounds in low concentrations needs attention, as well as the development of analytical techniques to detect possible new emerging contaminants.

As this first screening monitoring campaign was limited, a more thorough monitoring yielding information on statistical uncertainty and variability in time and space is recommended. In order to be able to better evaluate the presence of DOA in these waters, a more thorough derivation of human and ecotoxicological health standards for DOA in surface waters and drinking water is required.

An ecotoxicological risk assessment of DOA in the aquatic environment is recommended, especially at locations where these DOA are discharged into surface waters through STP effluents. Further research is necessary to investigate the contributions of STPs with respect to amounts of DOAs that are discharged into surface waters and the rivers Rhine and Meuse, what kinds of processes occur within the STP, their effects on the fate of the compounds and concentrations that are detected in STP effluent.

Further research into the presence of barbiturates in drinking water will help determine the necessity of adaptation measures. Information on effectiveness of drinking water treatment, sources and pathways will help focus possible adaptation measures.

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Appendix A UHPLC-MS/MS at UJI

In 2008, an analytical method was developed at the Research Institute for Pesticides and Water (IUPA), University Jaume I, Castellón (Spain) and validated for the analysis of various DOA and their metabolites in surface water and urban wastewater. This work is described by Bijlsma et al. (2009) and summarised in Figure A.1. In this study, sample pre-treatment was carried out at RIVM. Subsequently, the extracts were transported under dry-ice and analysed directly after arrival at the IUPA.

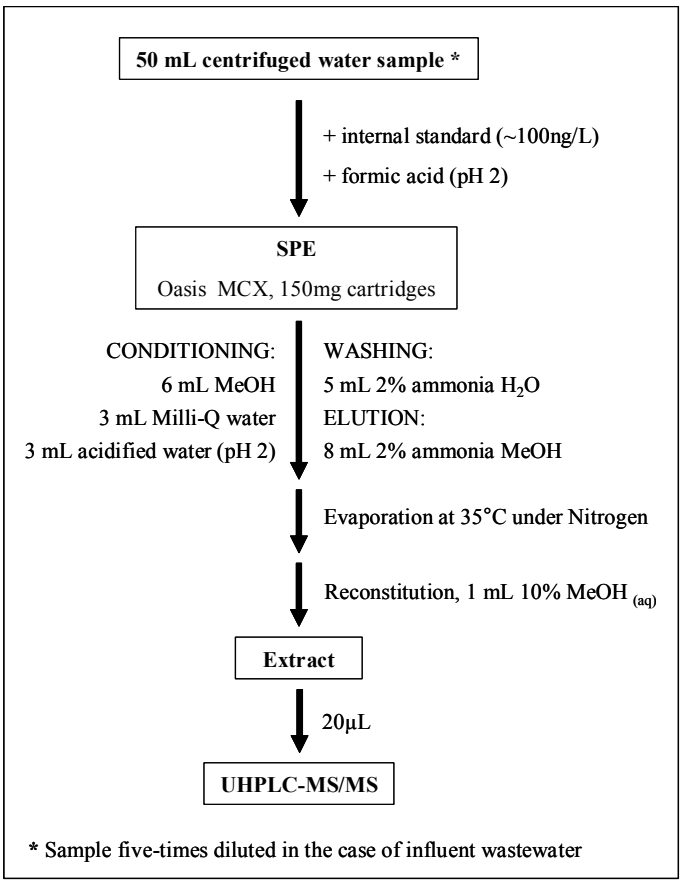

Figure A.1. Diagram of the recommended procedure.

A short explanation of the performed procedure

After the water samples were centrifuged and pH was adjusted to 2.0 with formic acid, selected compounds were extracted by means of solid-phase extraction (SPE) and analysed with UHPLC-MS/MS (TQD triple quadrupole mass spectrometer, Waters). The acquisition of three selected reaction monitoring (SRM) transitions per analyte allowed positive findings to be confirmed by accomplishment of ion ratios between the quantification transition and at least one additional specific confirmation transition (Table A.2). The limit of quantification (LOQ) is statistically determined, for a signal-to-noise ratio of ≥10, from the quantification transition.

This LOQ estimation is common in analytical methods applied to environmental monitoring. The most strict criterion, used in the earlier published work (Bijlsma et al., 2009), where an LOQ objective was established (the lowest concentration value that was fully validated applying the whole analytical procedure), was based on the SANCO guidelines (SANCO/2007/3131 and SANCO/825/00), which apply to residue analysis of pesticides. In this work, the LOQ estimation and confirmation criteria are appropriate and in accordance with EU directive 2002/657/EC. It must be emphasised that LOQs are highly dependent on the matrix water composition and on instrument sensitivity conditions. Therefore, the LOQs given should be taken as orientated estimated values, because some variations could be observed along the analysis of samples.

Table A.2. UHPLC-MS/MS parameters established for the SRM acquisition mode (quantification and confirmation transitions). For isotope labelled internal standards, only the quantification transition was acquired

Compounds	**Precursor ion (m/z) $[M + H]^+$**	**CV[a] (V)**	**CE[b] (eV)**	**Product ion[c] (m/z)**
Amphetamine	136.2	25	20	91.1
			10	119.1
			30	65.1
MDA	180.2	25	10	163.2
			20	105.1
			20	133.1
MDEA	208.3	35	25	105.1
			40	77.1
			25	135.1
MDMA	194.3	30	15	163.2
			25	105.1
			40	77.1
Methamphetamine	150.3	35	20	91.1
			10	119.1
			35	65.1
Cocaine	304.1	30	20	182.2
			30	82.0
			50	77.0
Cocaethylene	318.3	45	20	196.2
			30	82.0
			25	150.2
Benzoylecgonine	290.1	40	20	168.2
			30	82.0
			30	105.0
Norbenzoylecgonine	276.2	45	15	154.1
			20	136.1
			45	77.0
Norcocaine	290.1	30	15	136.1
			25	168.2
			35	68.0

THC-COOH	345.3	40	15	193.2
			25	299.3
			20	327.3
Amphetamine-d_6	142.2	25	20	93.1
MDA-d_5	185.2	25	10	168.2
MDEA-d_5	213.3	35	25	135.2
MDMA-d_5	199.3	30	15	165.3
Methamphetamine-d_5	155.3	35	20	92.3
Cocaine-d_3	307.1	30	20	185.3
Cocaethylene-d_8	326.3	45	20	204.3
Benzoylecgonine-d_3	293.1	40	20	171.2
THC-COOH-d_3	348.3	40	15	330.3

[a]CV, cone voltage; [b]CE, collision energy; [c]Top, product ion used for quantification (Q); Below, the
two product ions used for confirmation (q). For confirmation of the identity of the compound, at least
one confirmation transition has to accomplish the ion ratio (Q/q ratio).

Quality control and additional method characteristics

The quality control of the analysis was tested by injecting two quality control samples (QCs), i.e., a blank water sample (previously analysed) spiked at different concentrations (Table A.3), to every sequence of analysis. Water samples and QCs were analysed between two calibration curves. A data set was considered satisfactory when QC recoveries were in the range of 70 – 120% for each analyte.
Internal standards were used to compensate for possible losses resulting from the sample treatment and for correction of matrix effects (enhancement or suppression of the signal). Analyte isotope labelled internal standards were available for each selected drug of abuse, except for norcocaine and norbenzoylecgonine, since their labelled analogues were not commercially available. However, norcocaine could be quantified correctly by means of the isotope labelled internal standard of cocaine. For norbenzoylecgonine, no labelled standard was found suitable and therefore it was corrected using QC recoveries. This implies that measured concentrations of each drug of abuse best approaches reality.
Limits of quantification were sample-matrix dependent and are presented in Table A.3. QC recoveries were satisfactory for all compound/matrix combinations, with the only exception of QC 1 for methamphetamine in influent and effluent wastewater. Therefore, concentrations of methamphetamine in Table A.3 are corrected using these QC recoveries.

Table A.3. Concentration (ng/L) of DOA in quality control samples (QC) used for surface and wastewater

QC 1	**surface water**	**Effluent wastewater**	**Influent wastewater**
Amphetamine and amphetamine-type stimulants (ATS)	30	100	500
Cocaine and metabolites	10	30	150
THC-COOH	300	800	4000

Appendix B HPLC-MS/MS at RIVM

RIVM developed an analytical method based on the method that is described by Huerta-Fontela et al. (2007). This method is summarised in Figure B.1.

A short explanation of the performed procedure

The compounds were extracted from the water samples by means of solid-phase extraction and analysed with HPLC-MS/MS (Quattro Ultima triple quadrupole mass spectrometer, Waters).
The most abundant product ion of each compound was used for quantification and the second one for confirmation (Table B.1). The sample was considered positive when this ion ratio fell within the tolerance range described in EU directive 2002/657/EC.

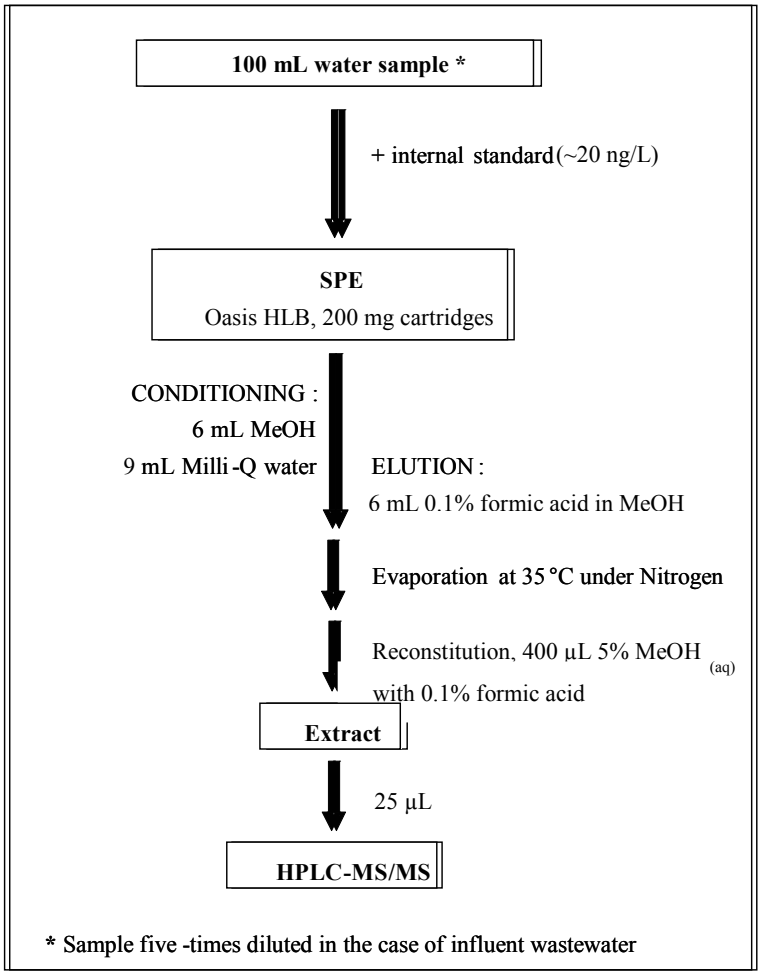

Figure B.1 Diagram of the RIVM procedure

Table B.1. HPLC-MS/MS parameters established for the SRM acquisition mode (quantification and confirmation transitions). For isotope labelled internal standards, only one transition was acquired

Compounds	**Precursor ion (m/z) $[M + H]^+$**	**CV[a] (V)**	**CE[b] (eV)**	**Product ion[c] (m/z)**
Amphetamine	136.4	15	15	91.4
			10	119.2
Methamphetamine	150.6	15	20	91.4
			10	119.2
MDA	180.4	20	10	163.4
			25	133.1
MDMA	194.5	40	10	163.3
			25	105.2
MDEA	208.5	15	15	163.3
			25	105.2
Ketamine	238.5	15	25	125.3
			15	220.3
Benzoylecgonine	290.6	10	20	168.4
			35	105.2
Cocaine	304.3	35	20	182.4
			35	105.2
Phencyclidine	244.6	25	15	86.2
			15	159.4
LSD	324.8	25	20	223.4
			30	208.2
Fentanyl	337.4	35	40	105.2
			25	188.4
Flunitrazepam	314.6	10	25	268.4
			35	239.2
Amphetamine-d_8	144.4	15	10	127.2
Methamphetamine-d_9	159.6	15	10	125.2
MDA-d_5	185.4	20	10	168.4
MDMA-d_5	199.5	40	10	165.3
MDEA-d_5	213.5	15	15	163.3
Ketamine-d_4	242.5	15	25	129.3
Benzoylecgonine-d_3	293.6	10	20	171.4
Cocaine-d_3	307.3	35	20	185.4
Phencyclidine-d_5	249.6	25	15	86.2
LSD-d_3	327.8	25	20	226.4
Fentanyl-d_5	342.4	35	40	105.2
Flunitrazepam-d_7	321.6	10	25	275.4

[a]CV, cone voltage; [b]CE, collision energy; [c]Top, product ion used for quantification (Q); Below, the product ion used for confirmation (q).

Quality control and additional method characteristics

The quality control of the analysis was tested by injecting three quality control samples (QCs), i.e., a tap water sample (previously analysed) spiked at different concentrations to every sequence of analysis (for the concentrations see table B.2). Water samples and QCs were analysed between two calibration curves.

Recovery experiments were performed by adding known concentrations of the compounds to the different types of water. These experiments were used for establishing the limit of quantification (LOQ), which is defined here as the lowest concentration at which the signal-to-noise ratio of the quantification ion is ≥10. Limits of quantification were compound and sample-matrix dependent.

Internal standards were used to compensate for possible losses resulting from the sample treatment and for correction of matrix effects (enhancement or suppression of the signal). Analyte isotope labelled internal standards were available for each selected drug of abuse.

Table B.2. Results of recovery experiments LC-MS/MS

Tap water (L.W.)

recovery (%)	amphetamine	methamphetamine	MDA	MDMA	MDEA	ketamine	benzoylecgonine	cocaine	phencyclidine	LSD	fentanyl	flunitrazepam
Spiked (ng/l)	5	5	5	5	5	5	5	5	5	15	5	15
L.W. + 5 ppt	77	89	86	94	85	67	101	87	110	77	98	98
L.W. + 5 ppt	84	84	98	96	92	79	102	96	126	91	86	103
L.W. + 5 ppt	82	73	91	92	95	124	90	96	93	95	82	92
L.W. + 5 ppt	76	73	99	93	96	129	91	95	94	101	86	95
L.W. + 5 ppt	104	68	91	92	88	91	88	94	108	98	86	87
L.W. + 5 ppt	101	73	98	100	94	97	100	100	107	111	92	97
L.W. + 5 ppt	62	72	87	100	92	108	106	101	138	97	110	99
L.W. + 5 ppt	73	69	84	103	92	108	101	99	138	91	104	98
L.W. + 5 ppt	66	81	92	111	94	100	88	91	98	93	95	105
avg. (n=9)	81	76	91	98	92	100	96	96	112	95	93	97
st.dev.	14	7	5	6	4	20	7	5	18	9	9	5
rel.st.dev. (%)	18	9	6	7	4	20	7	5	16	10	10	5
Spiked (ng/l)	25	25	25	25	25	25	25	25	25	75	25	75
L.W. + 25 ppt	94	89	86	100	96	101	101	98	121	93	102	97
L.W. + 25 ppt	85	86	85	93	91	92	96	92	105	96	87	94
L.W. + 25 ppt	93	86	102	94	101	97	95	97	112	93	96	97
L.W. + 25 ppt	91	88	103	105	98	108	100	100	109	100	96	102
L.W. + 25 ppt	89	87	103	98	96	100	103	98	118	103	96	101
avg. (n=5)	90	87	96	98	97	100	99	97	113	97	95	98
st.dev.	4	1	9	5	4	6	3	3	6	4	5	4
rel.st.dev. (%)	4	2	10	5	4	6	3	3	6	4	6	4
Spiked (ng/l)	125	125	125	125	125	125	125	125	125	375	125	375
L.W. + 125 ppt	90	80	92	96	96	99	97	96	108	97	91	95
L.W. + 125 ppt	90	87	96	88	95	84	93	89	107	91	90	92
L.W. + 125 ppt	82	87	98	97	92	93	96	93	107	90	87	89
L.W. + 125 ppt	91	96	106	101	99	99	95	95	101	96	94	96
avg. (n=4)	88	88	98	96	96	94	95	93	106	94	91	93
st.dev.	4	6	6	6	3	7	1	3	3	3	3	3
rel.st.dev. (%)	5	7	6	6	3	7	2	3	3	4	3	3
LOQ (ng/l)	5	3	5	2	2	2	2	4	1	10	3	4

Table B.2. Results of recovery experiments LC-MS/MS

Surface water (O.W)

recovery (%)	amphetamine	methamphetamine	MDA	MDMA	MDEA	ketamine	benzoylecgonine	cocaine	phencyclidine	LSD	fentanyl	flunitrazepam
Spiked (ng/l)	3	3	3	3	3	3	3	3	3	8	3	8
O.W. + 3 ppt		97		78	58	64	108		21		97	120
O.W. + 3 ppt		92		83	56	58	120		14		89	113
Spiked (ng/l)	5	5	5	5	5	5	5	5	5	15	5	15
O.W. + 5 ppt	77	98	85	95	80	81	126	94	66	103	87	106
O.W. + 5 ppt	72	96	85	101	75	87	115	99	79	107	101	105
Spiked (ng/l)	25	25	25	25	25	25	25	25	25	75	25	75
O.W. + 25 ppt	83	98	93	95	86	88	101	88	121	88	89	89
O.W. + 25 ppt	89	100	98	97	98	100	105	105	114	96	99	100
Spiked (ng/l)	125	125	125	125	125	125	125	125	125	375	125	375
O.W. + 125 ppt	88	87	92	98	90	94	101	92	127	91	84	89
O.W. + 125 ppt	95	96	102	109	95	105	109	103	127	96	97	95
LOQ (ng/l)	5	3	5	2	2	2	2	4	1	10	3	4

Table B.2. Results of recovery experiments LC-MS/MS

STP Influent

recovery (%)	amphetamine	methamphetamine	MDA	MDMA	MDEA	ketamine	benzoylecgonine	cocaine	phencyclidine	LSD	fentanyl	flunitrazepam
Spiked (ng/l)	25	25	25	25	25	25	25	25	25	75	25	75
influent + 25 ppt		87										
influent + 25 ppt		101										
Spiked (ng/l)	125	125	125	125	125	125	125	125	125	375	125	375
influent + 125 ppt	53	96		103	103	115		147		103		104
influent + 125 ppt	78	102		119	104	107		149		95		108
Spiked (ng/l)	625	625	625	625	625	625	625	625	625	1875	625	1875
influent + 625 ppt	94	106	120	109	110	111	144	121	125	123	88	103
influent + 625 ppt	97	89	116	103	109	116	164	115	135	116	90	98
Spiked (ng/l)	3125	3125	3125	3125	3125	3125	3125	3125	3125	9375	3125	9375
influent + 3125 ppt	91	90	111	100	105	107	109	100	123	104	103	91
influent + 3125 ppt	94	90	114	101	105	110	94	106	115	107	88	90
LOQ (ng/l)	116	23	324	41	46	51	323	57	141	135	417	106

Table B.2. Results of recovery experiments LC-MS/MS

STP effluent

recovery (%)	amphetamine	methamphetamine	MDA	MDMA	MDEA	ketamine	benzoylecgonine	cocaine	phencyclidine	LSD	fentanyl	flunitrazepam
Spiked (ng/l)	3	3	3	3	3	3	3	3	3	8	3	8
effluent + 3 ppt					91							
effluent + 3 ppt					91							
Spiked (ng/l)	5	5	5	5	5	5	5	5	5	15	5	15
effluent + 5 ppt					99					98	86	
effluent + 5 ppt					98					99	105	
Spiked (ng/l)	25	25	25	25	25	25	25	25	25	75	25	75
effluent + 25 ppt	104	96	108	119	111	110	93	100	117	119	94	108
effluent + 25 ppt	98	78	117	89	104	107	117	102	113	116	87	101
Spiked (ng/l)	125	125	125	125	125	125	125	125	125	375	125	375
effluent + 125 ppt	92	81	99	113	97	101	106	101	116	90	92	99
effluent + 125 ppt	97	99	110	124	109	109	110	107	143	111	95	105
LOQ (ng/l)	22	9	22	11	3	8	14	7	6	14	4	18

Appendix C HPLC-LTQ-Orbitrap MS at KWR

The samples were collected in ultra-clean, dark-green bottles and stored in the dark at 4 °C. Upon receiving of the bottles at the laboratory of KWR, all samples were filtered through a 0.20 µm polyethersulphon filter disposable setup (Nalgene).With the sewage treatment samples a 1.0 µm glass fibre pre-filter (Wattman) was used. The drinking water samples were left untouched. Prior to extraction, a set of 16 deuterated analogues were added to the sample at a concentration of 72 ng/L and the pH was adjusted to 7.

With the help of an automated large volume SPE system, samples were extracted by positive pressure using Oasis-HLB SPE stationary phase (150 mg, 60 µm) at a constant flow of 10 ml/min. The cartridge was dried with nitrogen for 15 min at a pressure of 1 bar. The analytes were eluted from the SPE column with 8 mL of methanol (1 ml/min). Finally, they were concentrated to a volume of 250 µl by means of an automated blow down apparatus (Barkey optocontrol) with heated nitrogen. To this extract 250 µl of pure water was added and mixed with the methanol and concentrated to <250 µl. The final extract was then made up, by weight to exactly 250 µl. As a final step, the volume was adjusted to 500 µl with methanol/water (20/80%) to achieve a final percentage of methanol of 10%. In this way larger volumes can be injected into the HPLC system without disrupting the performance of the compounds on the analytical HPLC column.

A hybrid LTQ-Orbtrap mass spectrometer (Thermo Electron provided with an ESI interface was interfaced to an Surveyor HPLC system (Thermo Electron) for the chromatographic separation). The LTQ-Orbitrap was automatically tuned and calibrated according to the factory tuning and calibration procedure. The needle of the ESI interface was a metal high-flow needle and the ion transfer capillary used was maintained at a temperature of 300 °C. The sheath, auxiliary and sweep gases were set to arbitrary units of 30 respectively, 10 and 10. A source voltage of 3.6 kV and a capillary voltage of 35 V was used in the positive mode. The tube lens was set to 70 V. Full-scan high-accuracy mass spectra were acquired in the range of 100–600 m/z with the resolution set at 30,000. Nominal product ions were acquired in a data-dependent acquisition mode.
In the negative mode, the axial position of the ESI interface was adjusted to obtain a higher sensitivity specifically for the barbiturates. With the help of a post column infusion of a 3% ammonium hydroxide solution in methanol/water (50/50%) full ionisation was facilitated to enhance sensitivity. From the extract 20 µl was introduced to the HPLC-Orbitrap MS system employing an Xbridge C18 column (150*2.1mm 3.5 µm) at 20 °C and using to following mobile phase composition: A, ultra pure water, 0.05% formic acid (pos); B, methanol 0.05% formic acid; linear gradient of 95% A to 0% in 20 min at 0.3 ml/min. In the negative mode, the following mobile phase composition was used: A, ultra pure water; B, methanol; linear gradient of 95% A to 0% in 20 min at 0.2 ml/min.

The analyte standards (Lipomed) were available in ready-to-use calibrated reference ampoules of 1 mL in either methanol, ethanol or acetonitrile, at a concentration of 1 g/L. From the ampoule 900 µL was diluted to a concentration of 36 mg/L in methanol according to the groups mentioned in the table above. The final mixture was made up by diluting aliquots from every group to a concentration of 3.6 mg/L. Working solutions for the calibration curves were made in methanol concentrations ranging from 7 pg/µL to 3 ng/µL. Before each

analytical run the standards were diluted 10 times with Ultra pure water (Millipore, MA, USA) resulting in a mix of 90% water and 10% methanol. For the deuterated standards the same procedure was followed except that they were added to all the calibration standards at a concentration level of 72 pg/µL, to assure no false positives are reported when adding the deuturated analogues. The purity of the deuterated analogues was investigated by creating "pseudo" extracts, spiked at the concentration level of 72 pg/µL increasing to 16 times this level to achieve sufficient sensitivity in case impurities were encountered. For three deuterated compounds (purity certificate listed in Table C.1) non-deuturated analogues were detected in the standard solutions supplied (see Table C.2).

Table C.1. Given certified purity

number	Compound	Lipomed certified purity
1	6-monoacetylmorphin-d3	98.7
2	benzoylecgonine-d3	99.63
3	Cocaine-d3	99.3

Table C.2. Contribution (expressed as % impurity) of non deuturated analogues in different solutions of deuterated standards of table C.1

	Number	1		2		3	
	ug/ int std in extract	6-monoacetylmorphine [ng]	% impurity	benzoylecgonine [ng]	% impurity	cocaine [ng]	% impurity
1	72	0.1	0.14%	0.12	0.17%	0.12	0.17%
2	144	0.18	0.13%	0.14	0.10%	0.11	0.08%
4	288	0.49	0.17%	0.4	0.14%	0.15	0.05%
8	576	1.2	0.21%	0.79	0.14%	0.37	0.06%
16	1152	2.6	0.23%	1.5	0.13%	0.75	0.07%
	Average impurity		0.17%		0.13%		0.08%

Identification and confirmation

Identification of the compounds was performed using the accurate mass of the protonated molecule within a mass window of 5 ppm together with one product ion (nominal mass). The retention times of the compounds were compared to those of the compounds in thecalibration standard solution of the final analysis. For confirmation of target compounds, LC relative retention time criteria (retention time window <2.5%) and mass spectrometric identification criteria need to be fulfilled. The latter are based on the concept of identification points (Commission Decision 2002/657/EC). For accurate mass screening using ToF or Orbitrap MS instruments, no criteria are described. Recently, some propositions for these type of instruments were made by Nielen et al. (2007). For high-resolution screening (resolution ≤ 20,000 and a mass accuracy ≤ 5 mDa) these authors proposed two identification points. Each product ion (low mass resolution MS) also contributes also two points. Thus acquiring a high resolution precursor ion in combination with at least one product ion and the LC relative retention time meets the minimum requirement of four identification points.

Table C.3 presents the accurate masses of precursor ions and nominal masses and relative abundance of product ions of non-deuterated DOA by LTQ-Orbitrap MS

Table C.3 Accurate masses of precursor ion and nominal masses and relative abundance of product ions of non-deuterated DOA by LTQ-Orbitrap MS [a]

Component	**Precursor**	**Ion**	**Ion 2**		
	m/z	**m/z**	**m/z**	**Abundance(%)**	**RSD**
	$[M+H]^+$				(n=16 -
Morphine	286.14334	201.1	229.1	51.9	8.9
Methcathinone	164.10699	146.1	133.1	1.7	20.9
Codeine	300.15942	215.2	243.1	47.7	6.1
Amphetamine	136.11208	119.1	91.1	0.5	14.6
6-Monoacetylmorphine	328.15433	211.2	268.2	73.7	6.9
Methamphetamine	150.12773	119.0	91.1	9.0	5.2
MDA	180.10191	163.2	-		
MDMA	194.11755	163.1	58.0	1.0	21.3
MDEA	208.13321	163.1	72.0	2.7	7.3
Ketamine	238.09932	220.1	207.1	23.9	5.3
Benzyl ecgonine	290.13868	168.2	272.2	4.8	12.9
Heroine	370.16490	328.2	268.2	99.1	2.1
Cocaine	304.15433	182.1	150.2	2.6	14.6
nordazepam(desmethyldiazepam)	271.06327	243.1	208.1	37.7	9.2
Ritalin	234.14886	84.0	174.2	0.3	60.7
metaCPP	197.08400	154.0	119.1	6.9	18.7
Fentanyl	337.22744	188.2	216.3	5.6	9.4
Meprobamate	219.13393	158.1	-		
Methadone	310.21654	265.1	247.2	0.1	54.3
Oxazepam	287.05818	269.1	241.1	3.9	8.6
desalk-flurazepam	289.05385	261.1	140.0	44.5	22.2
Temazepam	301.07383	283.0	255.2	9.2	5.0
Diazepam	285.07892	257.1	222.2	30.4	8.7
EDDP	278.19033	249.1	234.1	13.0	12.5
EDMP	264.17468	235.1	-		
11-OH-delta-9-THC	331.22677	313.3	-		
11-nor-9-Carboxy-THC	345.20604	327.2	299.3	6.1	8.2
delta-9-THC	315.23186	259.2	193.2	76.7	8.7
9-COOH-delta-9-THC	359.22169	-	-		
Barbital	183.07752	140.1			
Pentobarbital	225.12447	182.1			
Phenobarbital	231.07752	188.1			

[a] RSD: relative standard deviation in abundance of 2nd product ion; -, no stable product ion observed

[a] [M-H]- deprotonated ion

Method of determining the LOQ

Due to the principle of the data processing of the Orbitrap, the standard classical approaches to evaluate the limits of detection and LOQ cannot be applied (Kaufman et al., 2010). Therefore, a different approach was chosen which was proposed by de Voogt et al., (in press) and is based on the matrix suppression of the deuterated analogue and the identification criteria (EC, 2002) to reach enough confirmation points. Basically, the lowest standard visible in the calibration curve that meets all the identification criteria is used and divided by the matrix suppression calculated relative to tap water.
For analytes where no deuterated analogues were available, the following approach was used. In principle, the closest deuterated structure analogue was chosen. If not possible, either the deuterated analyte with a similar polarity or the closest eluting compound was selected.

Appendix D HPLC-MS/MS at UA

The determination of DOA and metabolites in influent wastewater by UA was performed using solid-phase extraction and hydrophilic interaction liquid chromatography-tandem mass spectrometry. An overview of the parameters of this analytical method is presented in Table D.1.

The simultaneous analysis of nine DOA (DOAs) and metabolites (amphetamine, methamphetamine, methylenedioxymethamphetamine, methadone, 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine, cocaine, benzoylecgonine, ecgonine methyl ester, 6-monoacetylmorphine) in influent wastewater was executed with solid-phase extraction (SPE) and hydrophilic interaction liquid chromatography (HILIC) coupled to tandem mass spectrometry (MS/MS) (van Nuijs et al., 2009c). Influent wastewater samples (50 mL) were brought to a pH of 2 and passed through a glass filter to remove solid particles. A SPE procedure on Oasis MCX cartridges was then applied. Conditioning of the cartridges was executed with consecutively 6 mL MeOH, 4 mL Milli-Q water and 4 mL Milli-Q water at pH = 2. The samples were then loaded, followed by drying of the cartridges under vacuum. Elution was performed with 4 mL of MeOH and 4 mL of 5% NH3 in MeOH. After SPE, the eluate was evaporated to dryness under a nitrogen stream and the residue was re-dissolved in 100 µL AcN and 100 µL AcN/ammonium acetate 5 mM in water (90/10, v/v). The extract was transferred to a centrifugal filter tube for a second filtering step. The resulting extract was analysed with the optimised HILIC-MS/MS system. The LC system consisted of an Agilent 1200 series binary pump and auto-sampler. Separation was achieved with a Phenomenex Luna HILIC (150 mm × 3 mm, 5 µm) column and a mobile phase composed by (A) ammonium acetate 5 mM in milli-Q water and (B) AcN using a gradient as follows: 0–0.5 min: 95% B; 0.5–6.5 min: 95%–50% B; 6.5-7.5 min: 50% B; 7.5–8 min: restoring the initial conditions (95% B); 8–14 min: 95% B for column equilibration. The flow rate was 0.4 mL/min and the injection volume was 5 µL. The MS system was an Agilent 6410 triple quadrupole mass spectrometer with an electrospray interface, operating in positive ionisation mode. Drying gas temperature was 350 °C and the nebuliser pressure was 35 psi (nitrogen). Quantitative analyses were performed in multiple reaction monitoring (MRM) mode and for each compound, the most abundant MRM transition was used for quantification (quantifier), while the other transition was used for confirmation (qualifier). The detected analytes were considered confirmed if the retention time did not differ more than ± 0.4 minutes from reference standards and if the ratio quantifier/qualifier in the extracted samples was not outside the range of ± 20% of this ratio in reference standards. Multi-level calibration curves (7 points) were generated for each analyte by spiking 50 mL blank surface water with different working standard mixtures of the analytes and a fixed amount of the deuterated internal standard mixture solution. Spiked surface water samples (at two concentration levels; low and high) were used as quality control samples

Method of determining the LOQ

The LOQ was set as the lowest point in the calibration curve of each compound. Care was also taken that the signal-to-noise ratio was no lower than 10, as recommended in the ICH guidelines

Table D.1. Overview of parameters of analytical method UA

				Quantifier		Qualifier	
	Retention time (min)	Precursor ion (m/z)	Fragmenter voltage(V)	Product ion (m/z)	Collision energy (V)	Product ion (m/z)	Collision energy (V)
6-Monoacetylmorphine	4,27	328.2	80	165.1	40	211.1	30
6-Monoacetylmorphine-d3	4.56	331.2	80	165.1	40		
benzoylecgonine	5.12	290.2	80	168	15	105	30
benzoylecgonine-d3	5.15	293	80	171	15		
Cocaine	4.71	304.2	80	182	15	82	40
Cocaine-d3	5.04	307	80	185	15		
Methadone	6.16	310.2	80	265.1	15	105.1	25
Methadone-d9	6.2	319.2	80	105	30		
EDDP	6.24	278	80	234.1	30	186.1	35
EDDP-d3	6.24	281	80	234	30		
Ecgonine methylester	6.65	200.1	80	182.1	20	82	20
Ecgonine methylester-d3	6.7	203	80	185	20		
MDMA	6.61	194.1	80	163.1	10	105.1	15
MDMA-d5	6.62	199.1	80	165.1	10		
Amphetamine	6.76	136	80	91	15	119	5
Amphetamine-d8	6.77	144	80	127	5		
Methamphetamine	6.64	150	80	91	15	119	5
Methamphetamine-d8	6.65	158.1	80	93.1	15		

Appendix E Monitoring results surface waters and drinking water

LEGEND - below LOQ			**Laboratory**	UJI	RIVM	KWR	UJI	RIVM	KWR	UJI	RIVM	KWR	UJI	RIVM	KWR	UJI	RIVM	KWR	UJI	RIVM	KWR
< detected but not quantified (below LOQ but above LOD)			**LOQ (ng/l)**	10	5	1	15	3	1	17	5	2	10	2	2	13	2	1	3	4	1
Description sampling point	**water type**	**company**	**date**	amfetamine	amfetamine	amfetamine	metamfetamine	metamfetamine	metamfetamine	MDA	MDA	MDA	MDMA	MDMA	MDMA	MDEA	MDEA	MDEA	cocaine	cocaine	cocaine
Andijk - IJsselmeer - PWN	surface water intake	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Andijk - IJsselmeer - PWN - ruw	raw	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Andijk - IJsselmeer - PWN - rein	finished	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haringvliet - Scheelhoek - Evides (Stellendam)	surface water intake	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haamstede - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haamstede - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ouddorp - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ouddorp - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bergsche Maas Biesbosch Keizersveer	surface water intake	Evides	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	<	-	-	-	-	-	-
Rotterdam-Berenplaat - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rotterdam-Berenplaat - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rotterdam-Kralingen - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rotterdam-Kralingen - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drentse Aa - de Punt - W Groningen	surface water intake	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Groningen - De Punt - W Groningen - ruw	raw	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Groningen - De Punt - W Groningen - rein	finished	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkanaal Nieuwegein	surface water intake	Waternet	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
Leiduin - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leiduin na ozon zuiveringsstap	raw, after ozone tr step	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Leiduin - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bethunepolder	surface water intake	Waternet	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Amsterdam Rijn kanaal / Nieuwersluis	water intake (summer)	Waternet	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-
Weesperkarspel - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weesperkarspel - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Brakel afgedamde Maas	surface water intake	Dunea	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Scheveningen - na duin ruw - DHZ	raw	Dunea	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Scheveningen - rein - DHZ	finished	Dunea	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heel lateraalkanaal Maas - WML - opp.water	surface water intake	WML	22-10-2009	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-
Heel lateraalkanaal Maas - WML - ruw	raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heel lateraalkanaal Maas - WML - rein	finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roosteren - ruw	bankfiltrate - raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roosteren - rein	bankfiltrate - finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - ruw	bankfiltrate - raw	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - rein	bankfiltrate - finished	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hendrik Ido Ambacht - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hendrik Ido Ambacht - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkerkerk - schuwacht - tiendweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkerkerk - schuwacht - tiendweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ridderkerk Reijerwaard Kievitsweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ridderkerk Reijerwaard Kievitsweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nieuw Lekkerland - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nieuw Lekkerland - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zwolle engelse werk (IJssel) - ruw	bankfiltrate - raw	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zwolle engelse werk (IJssel) - rein	bankfiltrate - finished	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lobith - Rijn (Tolkamer)	surface water	RWS	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Eijsden - Maas	surface water	RWS	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	1
Haringvliet - Maas	surface water	RWS	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Andijk - Rijn	surface water	RWS	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Maassluis - Rijn	surface water	RWS	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	<	-	-	-	-	-	-

LEGEND - below LOQ			Laboratory	UJI	RIVM	KWR	UJI	UJI	UJI	UJI	KWR	KWR	KWR	RIVM	KWR	KWR	KWR	KWR	RIVM	KWR	KWR
< detected but not quantified (below LOQ but above LOD)			LOQ (ng/l)	2	2	1	1	6	7	167	10	10	2375	4	1	1	1	1	3	-	1
Description sampling point	water type	company	date	benzoylecgonine (BE)	benzoylecgonine (BE)	benzoylecgonine (BE)	cocaethylene (CE)	norbenzoylecgonine	norcocaine	11-nor-9-Carboxy-THC (THC-COOH)	11-nor-9-Carboxy-THC (THC-COOH)	11-OH-Δ9-THC	Δ9-THC	flunitrazepam / rohypnol	diazepam	nordiazepam	oxazepam	temazepam	fentanyl	fentanyl	heroine
Andijk - IJsselmeer - PWN	surface water intake	PWN	14-10-2009	-	-	3	-	-	-	-	-	-	-	-	-	-	13	6	-	-	-
Andijk - IJsselmeer - PWN - ruw	raw	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	8	3	-	-	-
Andijk - IJsselmeer - PWN - rein	finished	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haringvliet - Scheelhoek - Evides (Stellendam)	surface water intake	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	11	4	-	-	-
Haamstede - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	3	1	-	-	-
Haamstede - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ouddorp - Evides - ruw	raw	Evides	15-10-2009	-	-	1	-	-	-	-	-	-	-	-	-	-	11	3	-	-	-
Ouddorp - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bergsche Maas Biesbosch Keizersveer	surface water intake	Evides	5-10-2009	3	3	4	-	-	-	-	-	-	-	-	-	-	62	28	-	-	-
Rotterdam-Berenplaat - Evides - ruw	raw	Evides	15-10-2009	-	-	3	-	-	-	-	-	-	-	-	-	-	13	10	-	-	-
Rotterdam-Berenplaat - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rotterdam-Kralingen - Evides - ruw	raw	Evides	15-10-2009	-	-	2	-	-	-	-	-	-	-	-	-	-	13	9	-	-	-
Rotterdam-Kralingen - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Drentse Aa - de Punt - W Groningen	surface water intake	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Groningen - De Punt - W Groningen - ruw	raw	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Groningen - De Punt - W Groningen - rein	finished	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkanaal Nieuwegein	surface water intake	Waternet	5-10-2009	-	-	2	-	-	-	-	-	-	-	-	-	-	60	32	-	-	-
Leiduin - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	1	-	-	-	-	-	-	-	-	-	-	4	2	-	-	-
Leiduin na ozon zuiveringsstap	raw, after ozone tr step	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	3	-	-	-	-
Leiduin - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bethunepolder	surface water intake	Waternet	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Amsterdam Rijn kanaal / Nieuwersluis	water intake (summer)	Waternet	5-10-2009	2	2	3	-	-	-	-	-	-	-	-	-	-	68	32	-	-	-
Weesperkarspel - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Weesperkarspel - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Brakel afgedamde Maas	surface water intake	Dunea	5-10-2009	-	-	3	-	-	-	-	-	-	-	-	-	-	22	9	-	-	-
Scheveningen - na duin ruw - DHZ	raw	Dunea	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	4	2	-	-	-
Scheveningen - rein - DHZ	finished	Dunea	28-10-2009	-	-	<	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heel lateraalkanaal Maas - WML - opp.water	surface water intake	WML	22-10-2009	8	8	9	-	-	-	-	-	-	-	-	-	-	29	13	-	-	-
Heel lateraalkanaal Maas - WML - ruw	raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Heel lateraalkanaal Maas - WML - rein	finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roosteren - ruw	bankfiltrate - raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roosteren - rein	bankfiltrate - finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - ruw	bankfiltrate - raw	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - rein	bankfiltrate - finished	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hendrik Ido Ambacht - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Hendrik Ido Ambacht - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkerkerk - schuwacht - tiendweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lekkerkerk - schuwacht - tiendweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ridderkerk Reijerwaard Kievitsweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Ridderkerk Reijerwaard Kievitsweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nieuw Lekkerland - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nieuw Lekkerland - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zwolle engelse werk (IJssel) - ruw	bankfiltrate - raw	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Zwolle engelse werk (IJssel) - rein	bankfiltrate - finished	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lobith - Rijn (Tolkamer)	surface water	RWS	5-10-2009	2	2	3	-	-	-	-	-	-	-	-	-	-	20	4	-	-	-
Eijsden - Maas	surface water	RWS	22-10-2009	12	16	15	-	-	-	-	-	-	-	-	-	-	27	3	-	-	-
Haringvliet - Maas	surface water	RWS	15-10-2009	-	-	1	-	-	-	-	-	-	-	-	-	-	9	3	-	-	-
Andijk - Rijn	surface water	RWS	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	6	4	-	-	-
Maassluis - Rijn	surface water	RWS	20-10-2009	2	2	3	-	-	-	-	-	-	-	-	-	-	23	6	-	-	-

LEGEND - below LOQ < detected but not quantified (below LOQ but above LOD)			Laboratory	KWR	KWR	KWR	KWR	RIVM	KWR	KWR	KWR	KWR	KWR	RIVM	RIVM	KWR	KWR	KWR	KWR
			LOQ (ng/l)	1	1	1	1	2	1	-	1	1	1	1	10	2	4	4	1
Description sampling point	water type	company	date	6-monoacetyl morphine (6-MAM)	codeine	morphine	methadon	ketamine	ketamine	mepridine	meta-CPP	methadrithmone	ritalin	phenydidine (PCP)	LSD	pentobarbital	phenobarbital	barbital	Desalkylflurazepam
Andijk - IJsselmeer - PWN	surface water intake	PWN	14-10-2009	-	-	-	<	-	-	-	-	-	-	-	-	-	7	<	-
Andijk - IJsselmeer - PWN - ruw	raw	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	7	-	-
Andijk - IJsselmeer - PWN - rein	finished	PWN	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Haringvliet - Scheelhoek - Evides (Stellendam)	surface water intake	Evides	15-10-2009	-	-	-	<	-	-	-	-	-	-	-	-	-	9	-	-
Haamstede - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	5	-	-
Haamstede - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Ouddorp - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	<	9	-	-
Ouddorp - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Bergsche Maas Biesbosch Keizersveer	surface water intake	Evides	5-10-2009	-	<	-	<	-	-	-	-	-	-	-	-	-	26	-	-
Rotterdam-Berenplaat - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	9	-	-
Rotterdam-Berenplaat - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Rotterdam-Kralingen - Evides - ruw	raw	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	10	-	-
Rotterdam-Kralingen - Evides - rein	finished	Evides	15-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Drentse Aa - de Punt - W Groningen	surface water intake	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	-
Groningen - De Punt - W Groningen - ruw	raw	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	8	-
Groningen - De Punt - W Groningen - rein	finished	WGron	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-
Lekkanaal Nieuwegein	surface water intake	Waternet	5-10-2009	-	4	-	<	-	-	-	-	-	-	-	-	<	12	-	-
Leiduin - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	<	6	-	-
Leiduin na ozon zuiveringsstap	raw, after ozone tr step	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	4	-	-
Leiduin - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bethunepolder	surface water intake	Waternet	5-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	23	12	-
Amsterdam Rijn kanaal / Nieuwersluis	water intake (summer)	Waternet	5-10-2009	-	6	-	2	-	-	-	-	-	-	-	-	4	13	<	-
Weesperkarspel - Waternet drinkwater - ruw	raw	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	23	11	-
Weesperkarspel - Waternet drinkwater - rein	finished	Waternet	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	7	-
Brakel afgedamde Maas	surface water intake	Dunea	5-10-2009	-	1	-	<	-	-	-	-	-	-	-	-	<	15	-	-
Scheveningen - na duin ruw - DHZ	raw	Dunea	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	12	-	-
Scheveningen - rein - DHZ	finished	Dunea	28-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	8	<	-
Heel lateraalkanaal Maas - WML - opp.water	surface water intake	WML	22-10-2009	-	7	-	<	-	-	-	-	-	-	-	-	-	25	-	-
Heel lateraalkanaal Maas - WML - ruw	raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Heel lateraalkanaal Maas - WML - rein	finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Roosteren - ruw	bankfiltrate - raw	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Roosteren - rein	bankfiltrate - finished	WML	22-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - ruw	bankfiltrate - raw	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-	-
Nijmegen Nieuwe Martkstraat (heumensoord) - rein	bankfiltrate - finished	Vitens	23-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	5	<	-
Hendrik Ido Ambacht - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	3	13	5	-
Hendrik Ido Ambacht - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	5	12	4	-
Lekkerkerk - schuwacht - tiendweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	10	27	12	-
Lekkerkerk - schuwacht - tiendweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	4	7	9	-
Ridderkerk Reijerwaard Kievitsweg - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	3	11	6	-
Ridderkerk Reijerwaard Kievitsweg - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	<	<	-
Nieuw Lekkerland - ruw	bankfiltrate - raw	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	4	14	7	-
Nieuw Lekkerland - rein	bankfiltrate - finished	Oasen	20-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	6	11	7	-
Zwolle engelse werk (IJssel) - ruw	bankfiltrate - raw	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	6	20	13	-
Zwolle engelse werk (IJssel) - rein	bankfiltrate - finished	Vitens	13-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<	-
Lobith - Rijn (Tolkamer)	surface water	RWS	5-10-2009	-	3	-	1	-	-	-	-	-	-	-	-	-	12	-	-
Eijsden - Maas	surface water	RWS	22-10-2009	-	23	7	2	-	-	-	-	-	-	-	-	-	27	-	-
Haringvliet - Maas	surface water	RWS	15-10-2009	-	-	-	<	-	-	-	-	-	-	-	-	-	8	-	-
Andijk - Rijn	surface water	RWS	14-10-2009	-	-	-	-	-	-	-	-	-	-	-	-	-	8	-	-
Maassluis - Rijn	surface water	RWS	20-10-2009	-	3	-	<	-	-	-	-	-	-	-	-	<	11	-	-

Appendix F Monitoring results for wastewater

Chemical class	Compound	Data	STP influent							
			A'dam West 11-okt-09	Apeldoorn 18-okt-09	Bosscherveld 4-okt-09	Culemborg 25-okt-09	Eindhoven 25-okt-09	Limmel 4-okt-09	s-Hertogenbosch 25-okt-09	Utrecht 1-nov-09
Amphetamines	**amphetamine**	Average of Conc (ng/l)	129	245	371	518	470	249	581	107
		StdDev of Conc (ng/l)	8	40	59	105	23	3	546	9
		≥ LOQ	3	3	2	2	3	2	3	4
		nr of labs	4	4	3	3	4	3	3	4
	metamphetamine	Average of Conc (ng/l)					24	278		
		StdDev of Conc (ng/l)						157		
		≥ LOQ					1	2		
		nr of labs	4	4	3	3	4	3	3	4
	MDA	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	3	3	3	3	3	3	3	3
	MDMA (Ecstasy)	Average of Conc (ng/l)	100	62	138	88	207	42	137	103
		StdDev of Conc (ng/l)	7	14	58		12		42	24
		≥ LOQ	2	3	2	1	3	1	2	3
		nr of labs	4	4	3	3	4	3	3	4
	MDEA	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	3	3	3	3	3	3	3	3
Barbiturates	**pentobarbital**	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	phenobarbital	Average of Conc (ng/l)		77	77		116	95	176	47
		StdDev of Conc (ng/l)								
		≥ LOQ		1	1		1	1	1	1
		nr of labs	1	1	1		1	1	1	1
	barbital	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
Benzodiazepins	**diazepam**	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	nordazepam (desmethyl-diazepam)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	oxazepam	Average of Conc (ng/l)	1021	1189	1363	2020	831	602	1442	866
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	temazepam	Average of Conc (ng/l)	455	255	813	450	302	371	493	278
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	desalkylflurazepam	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	flunitrazepam (rohypnol)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
Cannabinoids	**11-nor-9-Carboxy-THC (THC-COOH)**	Average of Conc (ng/l)	444		678	324	335	289	517	378
		StdDev of Conc (ng/l)								
		≥ LOQ	1		1	2	1	2	1	1
		nr of labs	2	2	2	2	2	2	2	2
	11-OH- Δ-9-THC	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	Δ-9-THC	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1

Chemical class	Compound	Data	STP influent							
			A'dam West 11-okt-09	Apeldoorn 18-okt-09	Bosscherveld 4-okt-09	Culemborg 25-okt-09	Eindhoven 25-okt-09	Limmel 4-okt-09	s-Hertogenbosch 25-okt-09	Utrecht 1-nov-09
Cocaïnics	**cocaïne**	Average of Conc (ng/l)	491	135	904	244	373	341	665	353
		StdDev of Conc (ng/l)	43	38	201	117	96	135	149	76
		≥ LOQ	3	3	2	2	3	2	2	3
		nr of labs	4	4	3	3	4	3	3	4
	benzoylecgonine (BE)	Average of Conc (ng/l)	2907	570	2412	947	1733	1181	2684	1193
		StdDev of Conc (ng/l)	321	51	274	194	370	206	279	204
		≥ LOQ	4	4	3	3	4	3	3	4
		nr of labs	4	4	3	3	4	3	3	4
	cocaethylene (CE)	Average of Conc (ng/l)	29	12	62	8		16	43	19
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1		1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	norbenzoylecgonine	Average of Conc (ng/l)	60		42	18	40	20	36	
		StdDev of Conc (ng/l)								
		≥ LOQ	1		1	1	1	1	1	
		nr of labs	1	1	1	1	1	1	1	1
	norcocaine	Average of Conc (ng/l)	20		39	10	14	19		15
		StdDev of Conc (ng/l)								
		≥ LOQ	1		1	1	1	1		1
		nr of labs	1	1	1	1	1	1	1	1
	ecgonine methylester	Average of Conc (ng/l)	312	84			249			183
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1			1			1
		nr of labs	1	1			1			1
Opiates	**phentanyl**	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	2	2	2	2	2	2	2	2
	heroïne	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	6-monoacetyl morphine (6-MAM)	Average of Conc (ng/l)								3
		StdDev of Conc (ng/l)								
		≥ LOQ								1
		nr of labs	2	2	1	1	2	1	1	2
	morphine	Average of Conc (ng/l)	634	1147	1464	480	377	553	364	300
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	codeïne	Average of Conc (ng/l)	975	412	800	417	434	681	618	300
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	methadon	Average of Conc (ng/l)	64	29			16			39
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1			1			1
		nr of labs	2	2	1	1	2	1	1	2
	EDDP	Average of Conc (ng/l)	135	73			36			91
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1			1			1
		nr of labs	1	1			1			1
Others	**ketamine**	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	2	2	2	2	2	2	2	2
	meprobate	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	meta-CPP (ecstasy)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	methacathinone	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	ritalin (methylphenidate)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	phencyclidine (PCP)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	LSD	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1

Chemical class	Compound	Data	STP Effluent							
			A'dam West 11-okt-09	Apeldoorn 18-okt-09	Bosscherveld 4-okt-09	Culemborg 25-okt-09	Eindhoven 25-okt-09	Limmel 4-okt-09	s-Hertogenbosch 25-okt-09	Utrecht 1-nov-09
Amphetamines	**amphetamine**	Average of Conc (ng/l)							15	
		StdDev of Conc (ng/l)							1	
		≥ LOQ							3	
		nr of labs	4	4	3	3	4	3		4
	metamphetamine	Average of Conc (ng/l)	35		13		30	62		
		StdDev of Conc (ng/l)	11		5		11	36		
		≥ LOQ	2		2		3	3		
		nr of labs	4	4	3	3	4	3	3	4
	MDA	Average of Conc (ng/l)							22	
		StdDev of Conc (ng/l)							1	
		≥ LOQ							3	
		nr of labs	3	3	3	3	3	3		3
	MDMA (Ecstasy)	Average of Conc (ng/l)	537	17	88	17	54	42	57	92
		StdDev of Conc (ng/l)	110	3	14	7	14	15	10	22
		≥ LOQ	4	3	3	3	4	3	3	4
		nr of labs	4	4	3	3	4	3	3	4
	MDEA	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	3	3	3	3	3	3	3	3
Barbiturates	**pentobarbital**	Average of Conc (ng/l)	10			9	6			25
		StdDev of Conc (ng/l)								
		≥ LOQ	1			1	1			1
		nr of labs	1	1	1	1	1	1	1	1
	phenobarbital	Average of Conc (ng/l)	37	63	101	35	191	117	145	81
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	barbital	Average of Conc (ng/l)	15							
		StdDev of Conc (ng/l)								
		≥ LOQ	1							
		nr of labs	1	1	1	1	1	1	1	1
Benzodiazepins	**diazepam**	Average of Conc (ng/l)	3		5		5	2	3	
		StdDev of Conc (ng/l)								
		≥ LOQ	1		1		1	1	1	
		nr of labs	1	1	1	1	1	1	1	1
	nordazepam (desmethyl-diazepam)	Average of Conc (ng/l)			31	13	18	21		14
		StdDev of Conc (ng/l)								
		≥ LOQ			1	1	1	1		1
		nr of labs	1	1	1	1	1	1	1	1
	oxazepam	Average of Conc (ng/l)	713	928	1498	1746	776	966	1398	952
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	temazepam	Average of Conc (ng/l)	397	389	1016	582	468	569	584	538
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	desalkylflurazepam	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	flunitrazepam (rohypnol)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
Cannabinoids	**11-nor-9-Carboxy-THC (THC-COOH)**	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	2	2	2	2	2	2	2	2
	11-OH- Δ-9-THC	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	Δ-9-THC	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1

Chemical class	Compound	Data	STP Effluent							
			A'dam West 11-okt-09	Apeldoorn 18-okt-09	Bosscherveld 4-okt-09	Culemborg 25-okt-09	Eindhoven 25-okt-09	Limmel 4-okt-09	s-Hertogenbosch 25-okt-09	Utrecht 1-nov-09
Cocaïnics	**cocaïne**	Average of Conc (ng/l)	2		4	4	2		11	1
		StdDev of Conc (ng/l)	1				1		5	
		≥ LOQ	2		1	1	2		2	1
		nr of labs	4	4	3	3	4	3	3	4
	benzoylecgonine (BE)	Average of Conc (ng/l)	21	7	22	18	9	7	84	26
		StdDev of Conc (ng/l)	8	2	8	2	3		6	10
		≥ LOQ	4	3	3	3	3	1	3	4
		nr of labs	4	4	3	3	4	3	3	4
	cocaethylene (CE)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	norbenzoylecgonine	Average of Conc (ng/l)	3			3			5	5
		StdDev of Conc (ng/l)								
		≥ LOQ	1			1			1	1
		nr of labs	1	1	1	1	1	1	1	1
	norcocaine	Average of Conc (ng/l)							4	
		StdDev of Conc (ng/l)								
		≥ LOQ							1	
		nr of labs	1	1	1	1	1	1	1	1
	ecgonine methylester	Average of Conc (ng/l)	6				3			3
		StdDev of Conc (ng/l)								
		≥ LOQ	1				1			1
		nr of labs	1				1			1
Opiates	**phentanyl**	Average of Conc (ng/l)		8						
		StdDev of Conc (ng/l)		6						
		≥ LOQ		2						
		nr of labs	2	2	2	2	2	2	2	2
	heroïne	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	6-monoacetyl morphine (6-MAM)	Average of Conc (ng/l)	6							3
		StdDev of Conc (ng/l)	1							
		≥ LOQ	2							1
		nr of labs	2	2	1	1	2	1	1	2
	morphine	Average of Conc (ng/l)	51	20	35	16	7		17	68
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1		1	1
		nr of labs	1	1	1	1	1	1	1	1
	codeïne	Average of Conc (ng/l)	171	164	223	110	130	123	378	240
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1	1	1	1	1	1	1
		nr of labs	1	1	1	1	1	1	1	1
	methadon	Average of Conc (ng/l)	56	19	49	6	10	25	12	41
		StdDev of Conc (ng/l)	1	1						3
		≥ LOQ	2	2	1	1	2	1	1	2
		nr of labs	2	2	1	1	2	1	1	2
	EDDP	Average of Conc (ng/l)	128	60			25			78
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1			1			1
		nr of labs	1	1			1			1
Others	**ketamine**	Average of Conc (ng/l)	28	2		4	28		15	6
		StdDev of Conc (ng/l)	3						1	
		≥ LOQ	2	1		1	1		2	1
		nr of labs	2	2	2	2	2	2	2	2
	meprobate	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	meta-CPP (ecstasy)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	methacathinone	Average of Conc (ng/l)	4							
		StdDev of Conc (ng/l)								
		≥ LOQ	1							
		nr of labs	1	1	1	1	1	1	1	1
	ritalin (methylphenidate)	Average of Conc (ng/l)	2	7		2	9		3	8
		StdDev of Conc (ng/l)								
		≥ LOQ	1	1		1	1		1	1
		nr of labs	1	1	1	1	1	1	1	1
	phencyclidine (PCP)	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1
	LSD	Average of Conc (ng/l)								
		StdDev of Conc (ng/l)								
		≥ LOQ								
		nr of labs	1	1	1	1	1	1	1	1

Appendix G Cocaine load back-calculation method

Example back-calculation for benzoylecgonine, see also Emke et al. (2010)

Load benzoylecgonine as cocaine (Zuccato et al., 2005)

$$cocaine_{g/day} = \left(\frac{Liters_{total/day} * C_{Benzoylecgonine[ng/l]}}{10^9} \right) * 0.45_{DTR\,BE} * \left(\frac{303_{M-Cocaine}}{289_{M-benzoylecgonine}} \right)$$

Load as STP Inhabitant Equivalent (I.E.) = 136 grams O_2 demand

$$I.E._{(STP)} = \left(\frac{T.O.D. = (C.O.D. + 4.57 * Nkj)}{136} \right)$$

Combined representing consumption per 1000 I.E.

$$\frac{cocaine_{mg}}{1000_{I.E.}} = \left(\frac{cocaine_{g/day}}{I.E_{(STP)} * 10^6} \right)$$

Appendix H Provisional drinking water limits

Toxicological limits for party drugs in drinking water sources

Advice requested by:	Drs. N.G.F.M. van der Aa (RIVM/IMG)
Date requested:	17-03-2010
Date advice:	19-07-2010
Date of revision1:	16-11-2010
Advice preparation:	Dr B.M. van de Ven (RIVM/SIR)
Advice review:	Ing. P.J.C.M. Janssen (RIVM/SIR)
Project no. RIVM:	M/703719/10/BB
PORS no.:	12658

Method

In the present document, provisional toxicological limits for party drugs in drinking-water sources are determined, to be used within RIVM project M/703719/10/BB: exploring measurements in drinking water (sources). Limit derivation is based on allocation of 10% of the ADI (acceptable daily intake) or the MRL (maximum residue limit) for milk determined for veterinary medicines to drinking water. In the calculation, an average bodyweight of 60 kg and a drinking water intake of 2 litres/day are assumed. For drugs not used as a veterinary medicine, the SIR/SEC database was searched to determine if an existing ADI was available. When no ADI was available from this database, a limited literature search was performed in Toxnet (queries using the name of the drug and the words 'toxicity' and 'review'). Abstracts were screened for ADIs or toxicologically relevant data. If no ADI or MRL was available, a provisional drinking-water limit was determined from the lowest pharmacological effective dose and a safety factor of 100, an average body weight of 60 kg and a consumption of 2 litres of drinking water per day.

Although it is known that some drugs interact at pharmacologically effective doses, no information was available on their possible interaction at the level of the proposed drinking-water limits. Therefore, no attempt was made to determine drinking-water limits for combinations of drugs. Only for drugs belonging to the same chemical group that are known to have the same mechanism of action a drinking water limit was derived for the whole group.

Benzoylecgonine

CASnr: 519-09-5
Chemical name:(1R,2R,3S,5S)-3-(Benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid

Benzoylecgonine is a (O-demethylated) metabolite of cocaine, not used as a drug itself but found in blood and urine after cocaine use. No evaluation of benzoylecgonine is present in the SIR/RIVM database. No ADI or oral toxicological information was found. Only some comparative toxicological studies have been performed in order to assess whether cocaine metabolites are more or less toxic then cocaine itself. In a study of Morishima et al., it was determined that doses of benzoylecgonine necessary to produce mild neurobehavioral

changes in rat after intravenous administration, were 30-fold higher than those for cocaine and that benzoylecgonine was not lethal, even at doses 100 times greater than those of cocaine (Morishima et al., 1999). Infusion with benzoylecgonine resulted in later onset of convulsions and respiratory and circulatory arrest in rats than after infusion with cocaine (Metz and Virag, 1995). Furthermore, in vitro, benzoylecgonine inhibited the development of embryos to blasocysts only at higher concentrations than did cocaine (Kaufmann and Armant, 1992). These results indicate that benzoylecgonine is less toxic than cocaine. Based on this conclusion, the provisional drinking-water limit for cocaine of 0.02 mg/L (see below) will be safe for benzoylecgonine as well. Therefore, a provisional drinking-water limit for benzoylecgonine is proposed of 0.02 mg/L.

Cocaine

CASnr: 50-36-2
Synonym: Benzoylmethylecgonine
Chemical name: Methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid

Cocaine is a strong central nervous system stimulant that induces euphoric effects. No evaluation of cocaine is present in the SIR/RIVM database. Cocaine is not used as a veterinary drug. It is used in human medicine but only as topical anaesthetic for ophthalmological procedures and for membranes of the nose and throat (Baselt, 2004). Typical use levels for addicts to cocaine are not provided in literature. In the IPCS monograph on cocaine it is mentioned that "the therapeutic use rate" is 1 to 3 mg/kg bw (IPCS), without specification of the route of administration. In a study which investigates "low doses of oral cocaine", levels of 50 mg/ person were used (0.8 mg/kg bw/d) (Epstein et al., 1999). The effects of cocaine have been exhaustively investigated but most studies concentrate on abuse, overdose, addiction and treatment of addicts. No suitable toxicological data are available for the derivation of an ADI. Therefore, a provisional ADI is derived from the lowest known oral pharmacological dose level of 0.8 mg/kg bw/day, using a safety factor of 100. This leads to a provisional ADI of 0.008 mg/kg bw. Allocating 10% of this ADI to drinking-water, a provisional drinking-water limit is derived of 0.02 mg/L (0.008 mg/kg bw/d /10 * 60 kg bw / 2 L).

Norcocaine

CASnr: 18717-72-1
Chemical name: Methyl (1R,2R,3S,5S)-3-(benzoyloxy)-8-azabicyclo[3.2.1]octane-2-carboxylic acid

Norcocaine is a (N-demethylated) metabolite of cocaine, not used as a drug itself but found in blood and urine after cocaine use. No evaluation of norcocaine is present in the SIR/RIVM database. No ADI or oral toxicological information was found. Only a few comparative toxicological studies have been performed in order to assess whether cocaine metabolites are more or less toxic than cocaine itself. In a study of Morishima et al., it was determined that doses of norcocaine necessary to produce toxic effects were smaller than those of cocaine when administered systemically to rats (Morishima et al., 1999). In another study, norcocaine infusion resulted in earlier onset of convulsions and respiratory arrest in conscious rats than with cocaine. Onset of circulatory arrest was also earlier with norcocaine (Metz and Virag, 1995). Cocaine was found to produce

haemodynamic changes in rats intravenously administered by increase in the mean arterial and right arterial pressure and a decrease in the heart rate. Norcocaine was at least as potent as cocaine on these parameters (Mahlakaarto et al., 1998). In vitro norcocaine is at least as active as cocaine in inhibiting the uptake of noradrenaline into rat brain synaptosomes (Hawks et al., 1974). In another in vitro study, norcocaine had an inhibitory effect on mitochondrial respiration at a concentration in which cocaine did not have this effect (Boess et al., 2000). Norcocaine is somewhat more active than cocaine when administered intravenously. It is not known whether this is also the case when orally administered, as no data on absorption or bioavailability after oral dosing of norcocaine is available. Oral absorption of cocaine is 60–80%, the absolute bioavailability is 33% (Fattinger et al., 2000).

The provisional ADI for cocaine (0.008 mg/kg bw/d) can be used as provisional ADI for norcocaine, with an additional safety factor of 4, taking into account that norcocaine is more active than cocaine (factor 2) and that it might have a higher bioavailability after oral intake (factor 2). The provisional ADI is then 0.002 mg/kg bw/d. The provisional drinking-water limit for norcocaine is derived at (0.002 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.006 mg/L.

MDMA

CASnr: 42542-10-9
Synonyms: 3,4-Methylenedioxymethamphetamine; Ecstasy
Chemical name: N,alpha-dimethyl-1,3-benzodioxole-5-ethanamine

MDMA is a ring-substituted derivate of methamphetamine, formerly used in psychotherapy but nowadays only as an illicit drug because of its psychoactive effects (euphoria, increased energy, increased empathy, etc.). No evaluation of MDMA is present in the SIR/RIVM database. MDMA is not used as veterinary medicine. In its recreational use as a psychoactive agent, MDMA is usually taken in oral doses of 100–150 mg (1.7 to 2.5 mg/kg bw) (Baselt, 2004). Because of the lack of suitable toxicological data from the published literature to derive an ADI, a provisional ADI is derived from the lowest pharmacological oral dose level to which a safety factor of 100 is applied. This leads to a provisional ADI of 0.017 mg/kg bw. The provisional drinking-water limit can be derived at (0.017 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.05 mg/L

Methamphetamine

CASnr: 537-46-2
Chemical name: Benzeneethanamine, N,alpha-dimethyl-, (alphaS)-

Methamphetamine is a sympathomimetic amine with CNS stimulant activity. It causes increased activity and talkativeness, decreased appetite and a general sense of well-being. No evaluation of methamphetamine is present in the SIR/RIVM database. Methamphetamine is not used as a veterinary medicine but it is used as human medicine for use by children and adults as a treatment for ADHD (Attention Deficit Disorder with Hyperactivity) and exogenous obesity as well as off-label for the treatment of narcolepsy and treatment-resistant depression (Mitler et al., 1993). The usual effective oral dose is 20 to 25 mg daily in children aged 6 years and older (http://www.drugs.com/pro/desoxyn.html). With an estimated mean bodyweight of 40 kg for children, the lowest pharmacologically effective oral dose can be calculated to equal 0.5 mg/kg bw. Because of the lack of suitable toxicological data from the published literature to derive an ADI, a provisional

ADI is derived from the lowest pharmacological oral dose level of 0.5 mg/kg bw, to which a safety factor of 100 is applied. This leads to a provisional ADI of 0.005 mg/kg bw. The provisional drinking-water limit can be derived at (0.005 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.015 mg/L.

Ketamine

CASnr: 6740-88-1
Chemical name: Cyclohexanone, 2-(2-chlorophenyl)-2-(methylamino)-,

Ketamine is used as an analgesic and anaesthetic agent in human and veterinary medicine. Although used as veterinary medicine, no MRL or ADI has been derived because of insufficient data, limited use and rapid elimination. No evaluation of ketamine is present in the SIR/RIVM database. Available repeated dose toxicity studies for the evaluation as veterinary medicine included a study in rats, dosed intravenously with 2.5, 5 or 10 mg/kg bw/day for 6 weeks, in which a slight but not significant decrease of food intake and moderate weight gain depression were measured. Furthermore, some reprotoxicity studies were evaluated, with a NOAEL for reprotoxicity of 10 mg/kg bw/day (the only dose used in study) administered intravenously for 3 days (day 9, 10 and 11 premating) in rats, and NOAELs for reprotoxicity of 20 mg/kg bw/d in studies with rats and rabbits dosed five days (intramuscular) during organogenesis and five days (intramuscular) in the perinatal period in rats. No other repeated dose studies were available.
For induction of anaesthesia, doses of 1 to 4.5 mg/kg bw intravenously or 6.5 to 13 mg/kg bw intramuscularly are used (Baselt, 2004). Oral absorption of ketamine is 24% (Chong et al., 2009) and the main metabolite formed, norketamine, is less active than ketamine, which together suggests that at least a 4 times higher dose has to be used orally compared to intravenously. A study in which women were dosed orally with 7.5 mg/kg bw resulted in narcosis in 83% of the women (Amiot et al., 1987). As an illicit drug, typical usage doses are 50–100 mg intravenously (1.3–2.5 mg/kg bw) and 200–300 mg (3.3–5 mg/kg bw) orally (Dalgamo and Shewan, 1996). The anaesthetic and hallucinating properties after oral dosing occur at lower dose levels than the NOAELs found in the animal feeding studies (lowest NOAEL after oral absorption was 10 mg/kg bw/day). Therefore, as a starting point for the provisional ADI, the level of 3.3 mg/kg bw is taken as the lowest pharmacologically effective oral dose. To this level a safety factor of 100 is applied. The provisional ADI is then 0.033 mg/kg bw. The provisional drinking-water limit is derived at (0.033 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.1 mg/L.

Codeine

CASnr: 76-57-3
Synonyms: Methylmorphine
Chemical name: Morphinan-6-ol, 7,8-didehydro-4,5-epoxy-3-methoxy-17-methyl-, (5alpha,6alpha)-

Codeine is an opium alkaloid used as an antitussive in the treatment of coughs and as analgesic for the relief of moderate pain. The main effect is respiratory depression. Codeine is well absorbed after oral administration; bioavailability is about 50%. Codeine is not used as a veterinary medicine. No evaluation is present in the SIR/RIVM database. Repeated oral dose toxicological studies have been performed by NTP in rat and mouse; in each species a 14-day, a 3-month and a 2-year study was performed. The lowest NOAEL from these studies was 15 mg/kg bw/d, which was the NOAEL in the 2-year study in rat. No evidence of

carcinogenicity was found up to doses of 80 (rat) and 400 (mice) mg/kg bw/d in the 2-year feeding studies. In a hamster NTP teratology study with dosing (gavage) on gestation days 5 to 13, the NOAEL for codeine-induced developmental toxicity was 10 mg/kg bw, administered twice daily (= 20 mg/kg bw/d); in a NTP mice teratology study with dosing (gavage) on gestation days 6 to 15, the NOAEL was 75 mg/kg bw/d (National Toxicology Programme Technical Report Series, 1996).

Pharmacologically recommended doses are 1 to 2 mg/kg bw/day for antitussive effects lasting all day, and 1.5 to 3 mg/kg bw for analgesic effects (Farmacotherapeutisch kompas). The antitussive and analgesic effects occur at oral doses lower than the levels causing no observed effect in the animal toxicity studies (lowest NOAEL in animal studies was 15 mg/kg bw/day). Therefore, as a starting point for the provisional ADI, the lowest pharmacologically effective dose of 1 mg/kg bw is used, to which a safety factor of 100 is applied. This leads to a provisional ADI of 0.01 mg/kg bw. The provisional drinking-water limit is 0.01 mg/kg bw/d /10 * 60 kg bw / 2 L = 0.03 mg/L.

Morphine

CASnr: 57-27-2
Chemical name: Morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl-, (5alpha,6alpha)-

Morphine is an alkaloid of opium and is a phenanthrene derivative. It produces a wide spectrum of pharmacologic effects including analgesia, dysphoria, euphoria, somnolence and respiratory depression. It is used in human medicine as an oral narcotic pain reliever when needed for longer periods of time. The oral dose varies from 30 to 600 mg/day (Baselt, 2004) (0.5 to 10 mg/kg bw/d). No evaluation of morphine is present in the SIR/RIVM database. Morphine has been exhaustively studied but most studies concentrate on abuse, overdose, addiction and treatment of addicts. No suitable toxicological data in the published literature were found to derive an ADI. Therefore, a provisional ADI is derived from the lowest pharmacological oral dose level of 0.5 mg/kg bw/d. To this level, a safety factor of 100 is applied. This leads to a provisional ADI of 0.005 mg/kg bw. The provisional drinking-water limit is (0.005 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.015 mg/L.

Methadone

CASnr: 76-99-3
Chemical name: 3-Heptanone, 6-(dimethylamino)-4,4-diphenyl-methadone

Methadone possesses many of the pharmacological properties of morphine and is approximately equipotent as an analgesic via different administration routes (including the oral route). Unlike morphine, however, methadone produces marked sedative effects with repeated administration, as a result of drug accumulation. The oral bioavailability of methadone is 80% (Baselt, 2004). No evaluation of methadone is present in the SIR/RIVM database. Methadone is not used as veterinary medicine. It is used in human medicine as maintenance treatment of former heroin addicts and as an analgesic. The pharmacologically recommended oral dose is 20 mg/day (0.33 mg/kg bw/day) for analgesic effects lasting all day (http://www.drugs.com/dosage/methadone.html). In the literature, no repeated oral dose toxicity studies were found. Therefore, as a starting point for the provisional ADI, the lowest oral pharmacologically effective dose is used, to which a safety factor of 100 is applied. This leads to a

provisional ADI of 0.0033 mg/kg bw. The provisional drinking-water limit is 0.0033 mg/kg bw/d /10 * 60 kg bw / 2 L = 0.01 mg/L.

Oxazepam

CASnr: 604-75-1
Chemical name: 7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one

Oxazepam is a benzodiazepine used therapeutically as a sedative-hypnotic and anti-anxiety agent in human medicine. It is not used as a veterinary medicine. No evaluation was found in the SIR/RIVM database. Toxicological studies have been performed by NTP in mice (two 14-week and two 2-year studies) and rat (one 2-year study). The lowest dose tested was 10 mg/kg bw in mice (2-year study), which was related to increased incidences of hepatoblastoma and hepatocellular adenoma, follicular cell hyperplasia of the thyroid gland and thyroid gland follicular cell adenoma (NTP TR 443). In rat, the lowest tested dose was 25 mg/kg bw/d, which caused nephropathy (http://ntp.niehs.nih.gov/go/6079). Based on available information on genotoxicity (NTP TR 443; http://ntp.niehs.nih.gov/go/6079), oxazepam is considered to be a non-genotoxic substance. No ADI can be derived from the toxicological studies of NTP.

The pharmacologically effective dose via the oral route is 30–60 mg (Baselt, 2004) (0.5–1.0 mg/kg bw/d). The pharmacological effects occur at doses much lower than the levels tested in the animal toxicity studies. The provisional ADI is 0.005 mg/kg bw/d, derived from the lowest pharmacological dose of 0.5 mg/kg bw/d by applying a safety factor of 100. This ADI is somewhat higher than that of temazepam (see below), a structurally related compound with a same mechanism of action. Therefore, the provisional drinking-water limit derived for temazepam will be safe for oxazepam as well. Based on the same mechanism of action, a common drinking-water limit is derived for these two chemicals (see below).

Temazepam

CASnr: 846-50-4
Chemical name: 7-chloro 1,3-dihydro-3-hydroxyl-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

Temazepam is a benzodiazepine hypnotic agent. Temazepam is used on a short-term basis to treat insomnia. It is only used as a human medicine, not as a veterinary medicine. No evaluation is available in the RIVM/SIR database. Limited toxicological data are summarised by IARC (1996). In a 78-week feeding study in mice, the lowest dose of 10 mg/kg bw/d showed no adverse effects. In a 2-year rat feeding study, with doses of 10, 40 and 160 mg/kg bw, all treated males and the low-dose females had higher mortality than the controls. Toxicity tests lasting six months at doses of up to 120 mg/kg bw/d in beagle dogs and rats did not show significant organ toxicity. No ADI can be derived from these toxicity data. The pharmacologically effective dose via the oral route is 15–30 mg (Baselt, 2004) (0.25–0.5 mg/kg bw/d). The pharmacological effect occurs at doses much lower than the levels causing no observed effect in the animal toxicity studies. Therefore, as a starting point for the provisional ADI, the lowest pharmacologically effective dose of 0.25 mg/kg bw is used, to which a safety factor of 100 is applied. This leads to a provisional ADI of 0.0025 mg/kg bw. The

provisional drinking-water limit is 0.0025 mg/kg bw/d /10 * 60 kg bw / 2 L = 0.008 mg/L. Based on a common mechanism of action by temazepam and oxazepam, a common drinking-water limit is derived for these two chemicals (see below).

Provisional drinking-water limit for oxazepam and temazepam
Based on the lowest pharmacologically effective dose via the oral route of 0.25 mg/kg bw for temazepam, a provisional drinking-water limit of 0.008 mg/L is derived. This value applies to oxazepam and temazepam. When these compounds occur together in drinking-water, the sum should not exceed 0.008 mg/L.

Pentobarbital

CASnr: 76-74-4
Chemical name: 5-Ethyl-5-(1-methylbutyl)- 2,4,6(1H,3H,5H)-pyrimidinetrione

Pentobarbital belongs to the group of barbiturates which have a sedative action in animals and humans. In humans, pentobarbital is used against sleeping problems. It is also used before surgery to induce sleep. Further uses in human medicine are in emergency treatment of seizures and as an euthanatic agent (physician-assisted suicide).

For sedation, the recommended oral dose for adults is 100 mg (1.7 mg/kg bw). For children of > 1 year old 2–6 mg/kg bw/day is recommended, to be applied divided in three doses (http://www.drugs.com/dosage/pentobarbital.html). No evaluation is available in the RIVM/SIR database for pentobarbital. No toxicity data on pentobarbital were identified in the published literature. A provisional ADI can be derived from the lowest pharmacologically effective dose via the oral route of 1.7 mg/kg bw. Applying a safety factor of 100 leads to a provisional ADI of 0.017 mg/kg bw. The provisional drinking-water limit is (0.017 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.05 mg/L. Based on a common mechanism of action by pentobarbital, phenobarbital and barbital a common drinking-water limit is derived (see below) for these three chemicals.

Phenobarbital

CASnr: 50-06-6
Chemical name: 5-Ethyl-5-phenyl-2,4,6(1H,3H,5H)-pyrimidinetrione

Phenobarbital is a further barbiturate with a sedative action. It is used in human medicine for the treatment of epilepsy. It is not used as a veterinary medicine. No evaluation is available in the RIVM/SIR database for phenobarbital. The lowest pharmacological effective oral dose is 100 mg/day (1.7 mg/kg bw/d) (Farmacotherapeutisch kompas). With phenobarbital, a large number of animals studies has been carried out. These data are summarised by IARC (2001). Carcinogenicity data comprise animal studies and a number of human epidemiological studies. Based on these studies, IARC classified phenobarbital as possibly carcinogenic for humans (2B), based on inadequate evidence in humans and sufficient evidence in experimental animals. Genotoxicity data show an inconsistent pattern. Overall, IARC concludes, phenobarbital is considered not genotoxic.

Phenobarbital is a teratogen and developmental neurotoxicant in humans and experimental animals. Exposure of rats in utero induces long-term effects on hepatic drug-metabolising enzymes. Neuroendocrine effects on reproductive

function have been noted in exposed adult male rats and female hamsters. These effects were seen at relatively high dose levels, mostly applied via non-oral routes.

Based on available information, the pharmacologically active dosage range may be assumed to be considerably below the levels at which toxic effects occurred in animal studies. Thus, a provisional ADI can be derived from the lowest pharmacologically effective dose via the oral route of 1.7 mg/kg bw. Applying a safety factor of 100 leads to a provisional ADI of 0.017 mg/kg bw. The provisional drinking-water limit is (0.017 mg/kg bw/d /10 * 60 kg bw / 2 L =) 0.05 mg/L. Based on a common mechanism of action by pentobarbital, phenobarbital and barbital, a common drinking-water limit is derived for these three chemicals (see below).

Barbital

CASnr: 57-44-3
Chemical name: 5,5-Diethyl-2,4,6(1H,3H,5H)-pyrimidinetrione

No evaluation for barbital is available in the RIVM/SIR database. Barbital is a barbiturate that is no longer in use in human medicine (Martindale). As the therapeutic dose ten to fifteen grains (0.65–0.97 grams) is given (http://www.medic8.com/medicines/Barbital.html). The Ullmann Encyclopaedia of Industrial Chemistry report a hypnotic dose of 0.25 to 0.50 grams (The Ullmann Encyclopaedia of Industrial Chemistry, 2000). For a 60 kg adult, this equals 4.2 mg/kg bw. The pharmacological potency of barbital is lower than that of phenobarbital and pentobarbital. Based on this the provisional drinking-water limit for phenobarbital and pentobarbital, 0.05 mg/L will be safe for barbital as well. Based on a common mechanism of action by pentobarbital, phenobarbital and barbital, a common drinking-water limit is derived for these three chemicals (see below).

Provisional drinking-water limit for pentobarbital, phenobarbital and barbital

Based on the lowest pharmacologically effective dose via the oral route of 1.7 mg/kg bw for both pentobarbital and phenobarbital, a provisional drinking-water limit of 0.05 mg/L is derived. This value applies to pentobarbital, phenobarbital and barbital. When these compounds occur together in drinking-water the sum should not exceed 0.05 mg/L.

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