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Data-driven prioritization of chemicals for various water types using suspect screening LC-HRMS

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ABSTRACT

For the prioritization of more than 5200 anthropogenic chemicals authorized on the European market, we use a large scale liquid chromatography-high resolution mass spectrometry (LC-HRMS) suspect screening study. The prioritization is based on occurrence in 151 water samples including effluent, surface water, ground water and drinking water.

The suspect screening linked over 700 detected compounds with known accurate masses to one or multiple suspects. Using a prioritization threshold and removing false positives reduced this to 113 detected compounds linked to 174 suspects, 24 compounds reflect a confirmed structure by comparison with the pure reference standard. The prioritized compounds and suspects are relevant for detailed risk assessments after confirmation of their identity. Only one of the 174 prioritized compounds and suspects is mentioned in water quality regulations, and only 20% is mentioned on existing lists of potentially relevant chemicals. This shows the complementarity to commonly used target-based methods.

The semi-quantitative total concentration, expressed as internal standard equivalents of detected compounds linked to suspects, in effluents is approximately 10 times higher than in surface waters, while ground waters and drinking waters show the lowest response. The average retention time, a measure for hydrophobicity, of the detected compounds per sample decreased from effluent to surface- and groundwater to drinking water, confirming the occurrence of more polar compounds in drinking water. The semi-quantitative total concentrations exceed the conservative and precautionary threshold of toxicological concern. Therefore, adverse effects of mixtures cannot be neglected without a more thorough risk assessment.

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1. Introduction

1.1. Chemical use

Worldwide the production and use of chemicals increase (CEFIC, 2014). Globally, over 340.000 chemicals are registered and regulated via national and international authorities (Chemical Abstract Service, 2014). New chemicals enter the market continuously. Chemicals are widely used for various beneficial purposes. They are used e.g. as pesticides, pharmaceuticals, flame retardants, food additives, cosmetics, and coatings. These chemicals and their transformation products can enter the aqueous environment; entry routes include sewage treatment plant (STP) effluents, agriculture run-off and infiltration, incidental spills and atmospheric deposition.

Most attention is paid to well-studied chemicals (Brack et al., 2015). Researchers and policy-makers intend to focus on the most relevant chemicals that actually threaten water quality and affect human and ecological health. Ultimately the wish is to come to overarching and integrating principles for risk assessment, able to deal with all chemicals and all the varying location-specific circumstances (Hendriks, 2013). The current practice however is to assess risks per chemical.

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1.2. Risk assessment

Citizens perceive risks of chemicals associated with drinking water as high, compared to various chemical and microbiological contaminants within different parts of the food chain (Kher et al., 2013). For a relatively small number of chemicals, detailed risk assessments including sufficient underlying data are available. Even fewer chemicals are regulated by water quality legislations, such as in Europe the EU Water Framework Directive including the Groundwater Directive and the Drinking Water Directive (WHO, 2011; Van Wezel et al., 2010). For various other chemicals, preliminary drinking water guidelines are derived (de Jongh et al., 2012; Kroes et al., 2004; Mons et al., 2013; Bruce et al., 2010; Schriks et al., 2010). Furthermore, following the approach of the Threshold of Toxicological Concern (TTC, Kroes et al., 2004), conservative TTC based values have been established for drinking water. The TTC-based target value for individual genotoxic and steroid endocrine chemicals is 0.01 μg/L. For all other organic chemicals the target value is 0.1 μg/L. The target value for the total sum of genotoxic chemicals, the total sum of steroid hormones and the total sum of all other organic chemicals are 0.01, 0.01 and 1.0 μg/L, respectively (Mons et al., 2013).

1.3. Prioritization

Various prioritization schemes for chemicals are available in literature (Guillén et al., 2012). Most of them compare modelled or measured occurrence concentrations of chemicals with (eco)toxicological effects, to have a first insight in possible risks. Many approaches start from observations of occurrence in surface waters, based on monitoring data using target chemical analytical methods (Guillén et al., 2012; von der Ohe et al., 2011; Brack et al., 2012; Slobodnik et al., 2012; Loos et al., 2009). These prioritizations are sometimes performed on a continental scale, but often river-basin specific (Slobodnik et al., 2012; López-Doval et al., 2012). Other approaches rely on modelled exposure concentrations (Wambaugh et al., 2013; Judson et al., 2014). Not many prioritization schemes have been developed with a focus on risks for drinking water thus far. Examples are schemes developed for pharmaceuticals (Moschet et al., 2014; de Voogt et al., 2009) and for the contaminant candidate list (CCL) according to the unregulated contaminant monitoring rule in the Safe Drinking Water Act (EPA, 1999). Ultimately the various ways to prioritize chemicals may lead to revised priority substances, as defined under the EU Water Framework Directive (Carere et al., 2013).

1.4. LC-HRMS

Liquid chromatography-high resolution mass spectrometry (LC-HRMS) is increasingly used for the detection and quantification of chemicals in water (Hogenboom et al., 2009; Krauss et al., 2010). The method allows for a broader overview on the chemicals that are present in the environment than target analytical approaches do (ter Laak et al., 2012; Schymanski et al., 2014a; Chiaia-Hernandez et al., 2014; Schymanski et al., 2014b). Given the sensitivity and the broad application range of LC-HRMS it is possible to detect a large amount of chemicals in one analytical run. At the same time, chemicals will not be detected if they will not be isolated, separated and ionized during the analytical process. In suspect screening approaches, LC-HRMS data is screened for a (large) list of chemicals or 'suspects' (Moschet et al., 2014; Schymanski et al., 2014a; Moschet et al., 2013; Hug et al., 2014; Vergeynst et al., 2014; Vergeynst et al., 2015a, b), or for a specific group of chemicals such as pharmaceuticals or pesticides (Moschet et al., 2014; Vergeynst et al., 2014).

Identities of the chemicals can be confirmed using reference standards or NMR analysis (Van Leerdam et al., 2014). Using isotopic pattern matching and fragmentation pattern verification based on libraries or MS^n data, various lower levels of confidence can be discerned (Schymanski et al., 2014b; Zedda and Zwiener, 2012). Confidence on the identity of compounds can be communicated according to Schymanski et al. (2014b).

1.5. This study

Here, we use a large-scale suspect screening study to prioritize a plenitude of chemicals for their possible human health relevance towards (drinking) water. The suspect list includes over 5200 chemicals, including hardly studied chemicals, authorized for the European market via various regulations. The study includes 151 Dutch water samples from effluent, surface water, ground water and drinking water. Non-target LC-HRMS data from these samples were screened for the list of suspect chemicals. The TTC is used as a threshold to prioritize the encountered suspects. The prioritized chemicals were compared to the chemicals in existing priority lists, literature and water quality legislation.

2. Materials and methods

2.1. Selection of suspects

The suspect list is composed, based on anthropogenic chemicals authorized on the market via various European regulatory frameworks. Included are chemicals applied in industry in volumes above 1000, and from 100 to 1000, tons per year in Europe, as registered under the REACH legislation (Registration, Evaluation, Authorization and restriction of Chemicals, Regulation EC 1907/2006, data obtained via the European Chemical Agency ECHA (2015)). In addition, substances of very high concern (SVHC) as defined under REACH for their carcinogenicity, mutagenicity, reproductive toxicity, persistency or bioaccumulative properties are included (CMR and PBT). CMR compounds as defined under the CLP Regulation on classification, labelling and packaging of substances and mixtures (1272/2008) are included, completed by Dutch legislation on CMR compounds. Furthermore included are chemicals authorized on the Dutch market under the Plant Protection Product Regulation (1107/2009/EC) and Biocidal Product Regulation (528/2012/EC), obtained via the Dutch Board for the Authorization of Plant Protection Products and Biocides. Finally, human and veterinary pharmaceuticals as authorized under the EU Directives 2001/83/EC and 2001/82/EC and listed in previous research (Ter Laak, 2011) are included.

Mixtures, inorganic chemicals, metalloids and non-ionisable chemicals are excluded from the suspect list, leading to a number of 5219 chemicals (Section 3.1). Only compounds with at least one heteroatom are considered ionisable with ESI (*e.g.* N, S, O, and P). For each chemical, the structural formula, CAS number and accurate molecular mass were collected.

To study the complementary value of this prioritization method, all chemicals regulated by the EU Drinking Water Directive and EU Water Framework Directive, including the Priority Substances Directive, are included in the suspect list, as are chemicals listed as potentially relevant for ecosystem health by the Norman network (Brack et al., 2012) and for drinking water by IAWR/RIWA (Hin and Bannink, 2013a, b).

2.2. Water sampling and LC-HRMS analysis

The water sampling and LC-HRMS analysis were performed as described by Hogenboom et al. (2009). Samples were taken during

2007–2014. The 151 samples are distributed over the Netherlands (Fig. 1), and comprise 20 drinking waters, 39 ground waters, 73 surface waters and 19 industrial and STP effluents.

STP effluents are 24 h flow-corrected samples. The other water samples are grab samples. All samples were stored in the dark at 1–5 °C and pre-treated within one week after sampling, or (incidentally) directly frozen at −25 °C before pre-treatment. Samples were isolated using OASIS HLB columns as Solid Phase Extraction (SPE) material (Waters, Milford, MA, USA). 200 mL of effluents and 1 L of the other types of water were extracted. Water samples were acidified to pH 2.3 prior to the SPE. After loading, the SPE cartridges were washed, dried using nitrogen and eluted with acetonitrile. The eluate is reduced to 500 μL. As internal standards atrazine-d_5, bentazone-d_6, chloroxuron, benzotriazole-d_4, fenuron and neburon were added to each sample (0.5 μg/L). The internal standards for quantification estimates (atrazine-d_5 and bentazone-d_6) were selected due to the stable ionization response in different sample matrices. The other internal standards are used for retention time alignment.

The resulting sample extracts were analysed using Liquid Chromatography coupled to a Linear Ion Trap (LTQ) Orbitrap High Resolution Mass Spectrometer (Thermo Fisher Scientific, Bremen, Germany), in positive and negative ionization mode.

Full scan accurate mass spectra were recorded from 50 to 1300 Da at a resolution of 60,000–100,000 Full Width at Half Maximum (FWHM) at m/z 400. Data dependant MS^2 spectra were acquired at low resolution without the need to specify parent masses, only the most intense ions were analysed by MS^2. The product ions were generated in the LTQ trap at a normalized collision energy setting of 35% and using an isolation width of 2 Da.

Electrospray ionization (ESI) source conditions were: capillary voltage 4.0 kV (positive-ion measurements), 2.5 kV (negative-ion measurements), heated capillary temperature 300 °C, capillary voltage 24 V, tube lens 70 V.

The LC system consisted of an Accela UHPLC system and an Accela autosampler (Thermo Fisher Scientific). The chromatographic separation was performed on an Omnisphere C18 column (150 mm × 2.0 mm i.d., 3 μm, Varian-Chrompack, Middelburg, the Netherlands). The precolumn used was a C18 Guard column (4.0 mm × 3.0 mm i.d., Phenomenex). The columns were

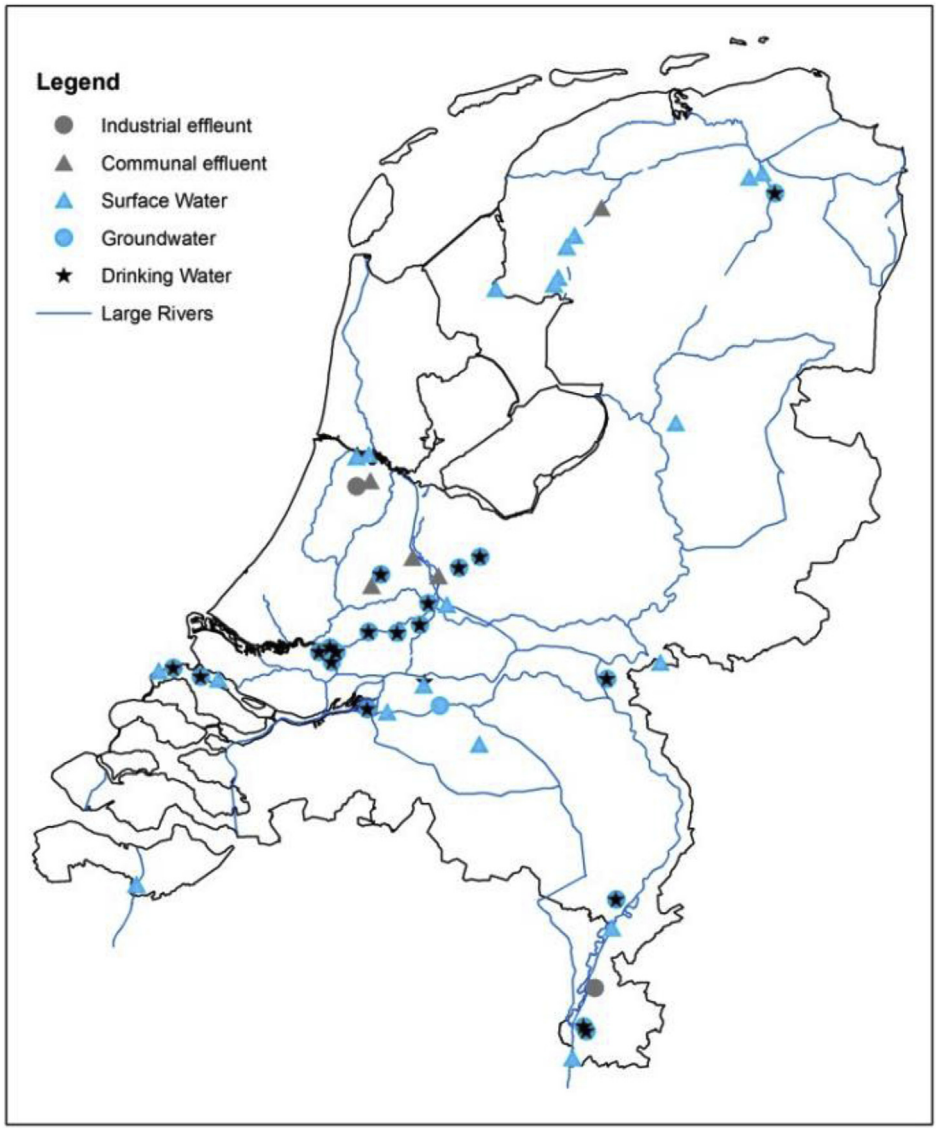

Fig. 1. Sampling locations for drinking waters, ground waters, surface waters and effluents.

maintained at 21 °C with a column thermostat. The injection volume was 5 μL.

In order to obtain comparable retention times in positive and negative ionisation modes, we used an identical linear gradient in both modes. The following linear gradient was applied: starting at 5% acetonitrile/95% water/0.05% formic acid (v/v/v) increasing to 100% acetonitrile with 0.05% formic acid in 40 min with a flow rate of 0.3 mL/min. The acid, although decreasing the ionization for some compounds in the negative ionization mode, equals the retention times for different compounds in negative and positive ionisation mode. The analytical column was re-equilibrated at starting conditions between consecutive runs for 15 min.

For the blank procedure, a sample of ultra-pure water (Millipore) with the same treatment and analysis as the samples was included in each analytical run. Additionally, for quantification purposes, a set of 67 regularly in water detected compounds were analysed within each analytical run (Tables S.1 and S.2).

2.3. Suspect screening and data interpretation

As chromatograms obtained in the period 2007 to 2014 are used in the present study, replacement or adjustment of the instrumental parts of the LC-HRMS system -such as columns, tubing or valves – might have led to minor changes in chromatography and retention time. MSXelarator software (MsMetrix Maarssen, The Netherlands) (Jacobs et al., 2013) was used to align the chromatograms based on internal standards to ensure comparability between samples. Reference peak warping uses accurate mass reference peaks to perform a non-linear retention time correction based on spline fitting. Only compounds eluting between 2 and 40 min were compared.

As no suitable internal standards were used at our laboratory for this applied method prior to 2010, data in the negative ionization mode were only used when obtained after 2010, i.e. 9 drinking waters, 14 ground waters, 29 surface waters and 14 effluents.

The recorded chromatograms were screened for the chemicals on the suspect list, using the MsXelerator software. For each individual file, all peaks are detected using an untargeted peak picking algorithm that operates on extracted ion currents. Basic chromatographic peak picking parameters like retention time, area, peak height, FWHM and signal to noise ratio are determined. Peaks having a signal to noise ratio smaller than 10 or an absolute threshold smaller than 100.000 counts were removed, to exclude small noisy peaks. Furthermore, the averaged mono-isotopic accurate mass is determined, based on the FWHM of the chromatographic peak. The mass spectra of the detected compounds were manually checked on possible adduct ions (sodium and ammonium).

Using a clustering algorithm all peaks from individual files are grouped into a table containing all results for all samples. The algorithm clusters peaks having the same accurate mass (± 5 ppm) and within the same retention time window (± 5 min).

The untargeted result table is screened against the list of suspects for which the accurate masses are known by screening for the accurate molecular ions $[M+H]^+$ and $[M-H]^-$ with a mass window of ± 5 ppm for the positive and negative ionization mode, without a retention time restriction.

Finally, peaks in the result table which are not present in the suspect list are subsequently removed from the table.

The proper functioning of the applied method has been confirmed by the recovery of the 67 out of 74 spiked target compounds in drinking water samples with a concentration of 0.1 μg/L.

The concentration of the compounds is expressed in terms of atrazine-d_5 or bentazone-d_6 equivalents (IS-eq) from the peak heights for all detected chemicals in the positive or negative ionization mode respectively, with a detection limit of 0.01 μg/L IS-eq. Due to extraction and ionisation differences the concentration in IS-eq does not reflect the exact concentration of the detected compounds; it is considered a semi-quantitative parameter that can be used to estimate the concentration of the compounds (see Section 4.2).

2.4. Prioritization and identification

To prioritize the detected compounds and the corresponding suspects for the different matrices, the following thresholds were chosen in semi-quantitative concentrations; a) 1.0 μg/L IS-eq for effluent, b) 0.1 μg/L IS-eq for surface water and c) 0.01 μg/L IS-eq for ground water and drinking water. The prioritization thresholds per compound are derived from the TTC for genotoxic and steroid endocrine chemicals, expected generic drinking water treatment efficiencies and expected generic dilution within the water cycle. The TTC is used here as a conservative first step in the prioritization process. In view of the large number of suspects and the generally limited available toxicological information, modes of toxicological action – genotoxicant, hormonal disruptor or other – are not differentiated for. A more in-depth risk assessment based on substance-specific toxicological data generally shows less conservative risk limits (Mons et al., 2013; Schriks et al., 2010), and will be performed in a follow-up.

As environmental samples were used with an unknown amount of chemicals, the purpose of this study is not to optimize false positives versus false negatives ratio (Vergeynst et al., 2015a). The mass spectrometry data of the prioritized detected compounds and the corresponding suspects were evaluated in order to increase the confidence level of identification. The detected compounds are classified into two of the five confidence levels for identification according to Schymanski et al. (2014b). First, an in-house LC-HRMS database on pure reference standards covering 155 chemicals, including 111 standards present in the suspect list (Table S.3), was used to unequivocally confirm chemical identity (confidence level 1 for identification). Based on these standards, differences in responses among chemicals are analysed. If the total isotopic patterns of the detected compounds and the suspects were similar (>90% similarity), these compounds were classified into identity confidence level 4.

Linked suspects with a different isotopic pattern were classified as false positives. It was not possible to retrieve compounds with confidence level 2 and 3 for identification, due to insufficient MS^2 data quality. In future research, the identity of the prioritized suspects with confidence level 4 for identification, will be confirmed by pure reference compounds and MS^2.

3. Results

3.1. Selection of suspects

The suspect list covers 5219 individual chemicals (Table 1). Some chemicals appear in multiple categories (for details see Table S.4). The suspects are anthropogenic and mostly parent compounds.

3.2. Priority compounds from suspects screening results

700 detected compounds with accurate masses retrieved with LC-HRMS in the 151 water samples can be linked to one or multiple suspects. In total 158 detected compounds are above the respective thresholds for prioritization (Table 2, Tables S.5 and S.6). The 158 detected compounds are linked to 243 suspects. Comparison with the pure reference compound (accurate mass, retention time and

Table 1
Composition of suspect list.

Suspects	Number of chemicals
Authorized chemicals	
REACH Registration list >1000 tons	2198
REACH Registration list 100–1000 tons	1922
REACH SVHC	68
CMR	181
Pesticides/Biocides	364
Human and veterinary pharmaceuticals	211
Chemicals in EU water quality regulation	
Drinking water directive	15
Priority substances directive	37
Potentially relevant chemicals	
Drinking water relevant chemicals IAWR/RIWA	81
Ecosystem relevant chemicals NORMAN	623

current research and will be performed in a follow up study. False negatives may also occur, *e.g.* due to extraction, separation or ionization problems (Vergeynst et al., 2015a). This is further quantified in Section 4.2.

The 113 prioritized compounds with their suspects, identity confidence level and the water type for which the compounds were prioritized are shown in Tables S.5 and S.6. Molecular formulas, accurate masses and ionisation modes are found in Table S.5. After confirmation of the identity, the prioritized compounds can be used for in-depth risk assessment based on substance-specific toxicological data and accurate quantification. If relevant, the confirmed compounds might be introduced in future monitoring programs or eventually risk management measures.

Table 2
Prioritized detected compounds, the number of suspects and the according identification confidence level.

Prioritized detected compounds	Linked suspects	Class name	Identification confidence level
158	243	Prioritized detected compounds	
24	24	Confirmed structures	1
89	150	Unequivocal molecular formula	4
45	67	False positives	Rejected

MS^2 data), revealed that 24 of the prioritized suspects have a confirmed structure (Table 3). This corresponds to confidence level 1 of the classification of Schymanski et al. (2014b). 89 detected compounds match to one or multiple suspects (level 4) that reflect the unequivocal molecular formula, based on more than 90% similarity of the isotopic pattern of the detected mass and the suspect (confidence level 4). Finally, 45 detected compounds were linked to suspects with a different molecular formula based on isotopic pattern analysis and can be considered as false positives. The (corrected) false positive rate is thus 28% or higher after identification of compounds currently classified into identity confidence level 4.

After removing the 45 false positives, 113 prioritized detected compounds remain prioritized, linked to 174 suspects, less than 3.5% of the suspect list. Most of the prioritized suspects have been detected in surface water in the positive ionisation mode (Table 4). The majority of the detected compounds are linked to only one suspect, although some detected compounds can be ascribed to multiple suspects (Tables 4 and 5). Compounds classified into identity confidence level 4 might still contain false positives and are candidates for further confirmation with pure reference standards (check of retention time and MS^2ions). The high number of suspects used here (5219) increases the coincidental matches and thus false positives. Therefore, identification of the suspects assigned to each peak is important. Further improvement of the confidence level of suspects not present in the database is outside the scope of the

3.3. Origin of prioritized suspects

Most of the 174 prioritized suspects are registered chemicals under REACH with a production rate above 100 tonnes/year (76% of all prioritized suspects), while pesticides and biocides account for 11% and pharmaceuticals for 6% of all prioritized suspects. This reflects the composition of the suspect list. A higher percentage of chemicals authorized as pesticides/biocides and pharmaceuticals is prioritized (both 5%), compared to the REACH chemicals with a production rate above 100 tonnes/year of which 3% is prioritized.

3.4. Fingerprinting

An overview of the prioritized suspects occurring in the various water matrices is given in Fig. 2. Each water type contains prioritized suspects being registered under REACH, pharmaceuticals and pesticides/biocides. In surface water, ground water and drinking water, fewer compounds are detected per sample compared to effluents. However, the contribution of ground- and drinking water to the prioritized detected compounds is substantial, due to lower prioritization thresholds.

3.5. Total concentrations of detected compounds in the samples

Due to differences in the isolation recovery and the ionization efficiency (Chalcraft et al., 2009; Gosetti et al., 2010; Bergman et al.,

Table 3
The 24 prioritized compounds with a confirmed structure.

Plant protection products	Pharmaceuticals	Industrial compounds
chloridazon	caffeine	1,2-benzisothiazol-3(2H)-on
dimethenamide P	carbamazepine 10,11-epoxide	4-Methyl-1H-benzotriazole
dimethomorf	metoprolol	benzotriazole
MCPA	N-acetylaminoantipyrine	tributyl phosphate
MCPP	oxazepam	triethyl phosphate
metolachloor	phenazone	triphenylphosphine oxide
N,N-Diethyltoluamide (DEET)	propyphenazone	tris(2-chloro-1-methylethyl) phosphate
simazine	tramadol	
terbuthylazine		

Table 4
The number of prioritized detected compounds and suspects above the respective thresholds per water type after removing the false positives.

Water type	Combined modes		Positive ionization mode		Negative ionization mode	
	Masses	Suspects	Masses	Suspects	Masses	Suspects
Effluent >1 μg/L	29	43	21	25	8	18
Surface water >0.1 μg/L	62	86	47	61	15	25
Ground water >0.01 μg/L	47	66	42	55	5	11
Drinking water >0.01 μg/L	28	50	14	17	14	33
All > threshold	113	174	76	100	37	74

Table 5
The number of suspects which can be linked to one detected compound with an accurate mass after removing the false positives.

	Effluent	Surface water	Ground water	Drinking water	All masses
1 suspect	21	46	37	19	79
2 suspects	3	9	4	2	14
3 suspects	4	5	5	4	15
4 suspects	1	2	–	1	3
5 suspects	–	–	–	1	1
6 suspects	–	–	1	1	1

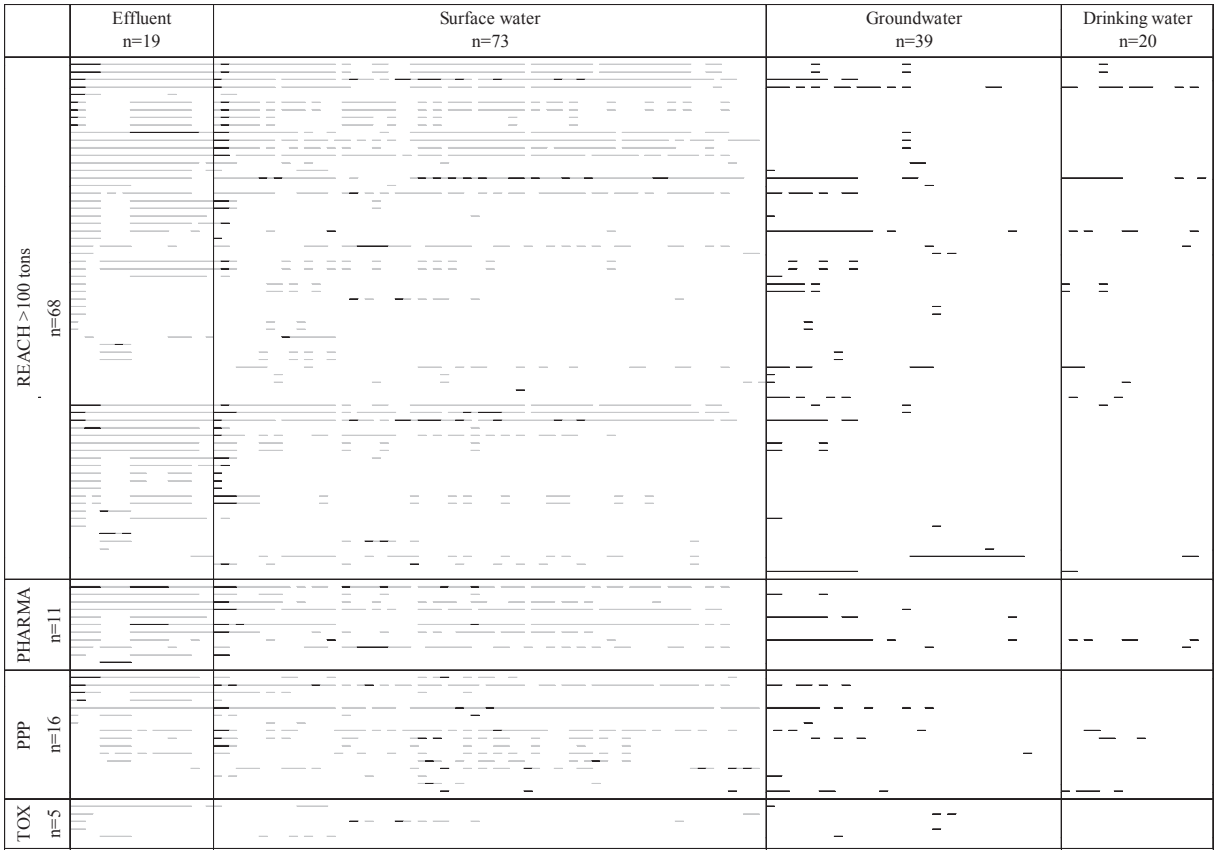

Fig. 2. Prioritized (black) and occurring below prioritization threshold (grey) suspects in all analysed water samples (positive ionization). Each row represents a prioritized suspect (n = number of suspects, in REACH, pharmaceuticals (PHARMA), pesticides/biocides (PPP) or substances of very high concern and CMR compounds (TOX). Each column represents a sample (n = number of samples) from different water types.

2013; Kruve et al., 2014), the total concentration expressed in μg/L IS-eq is to be considered a generic semi-quantitative parameter.

The semi-quantitative total concentration of all detected compounds (>0.01 μg/L IS-eq) linked to a suspect differs significantly between samples (ANOVA, $p \leq 0.0001$) (Fig. 3a,b). In effluent samples (14.75 ± 1.16 μg/L IS eq), the total concentration of the masses detected in the positive mode is approximately 10 times higher than the total concentration in surface water samples (1.55 ± 0.25 μg/L IS eq). Ground water (0.19 ± 0.03 μg/L IS eq) and drinking water (0.08 ± 0.02 μg/L IS eq) show the lowest total concentrations. The semi-quantitative total concentration of the detected compounds in the negative ionisation mode of different water types is slightly different to the positive mode (Fig. 3b). Only effluent (16.85 ± 6.45 μg/L IS-eq) differs significantly from surface

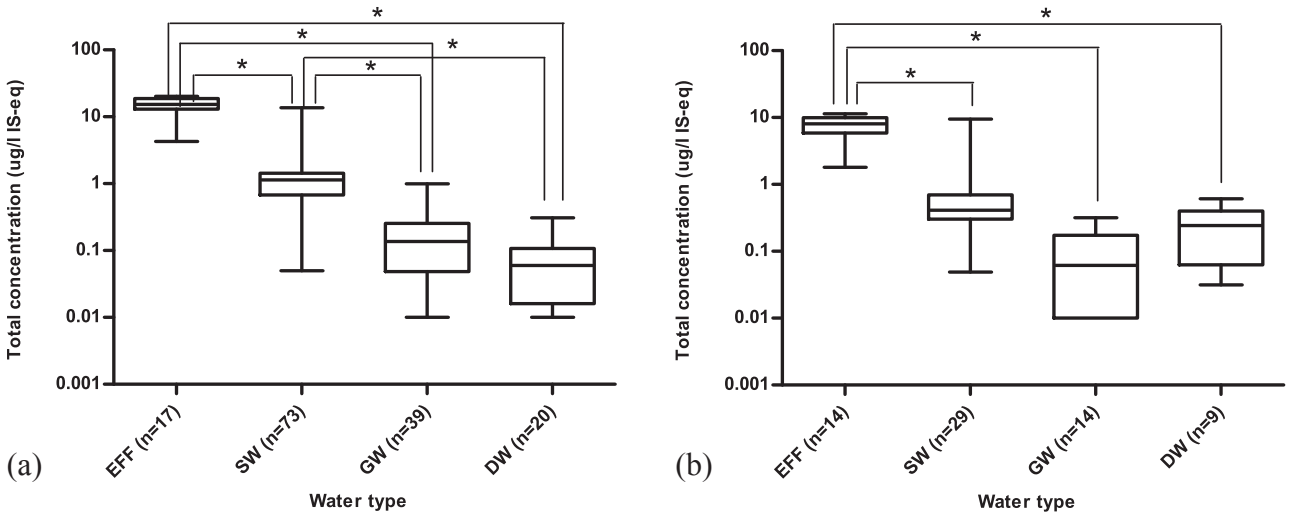

Fig. 3. Distribution of the semi-quantitative total concentration (IS-eq) of the masses detected in the positive (a) and negative (b) mode, linked to a suspect for the different water types (n is the number of water samples). The box represents the median, 25% and 75% percentile values. The whiskers extend to the minimum and maximum values. Combinations with significant different means are indicated with an asterisk (*).

water (1.03 ± 0.38 μg/L IS-eq), ground water (0.10 ± 0.03 μg/L IS-eq) and drinking water (0.25 ± 0.07 μg/L IS-eq) ($p < 0.0001$).

The semi-quantitative total concentration of the detected compounds linked to a suspect is an underestimation of the total concentration of all compounds present. However, the detected suspects are of anthropogenic origin and natural occurring substances and metabolites are therefore excluded. The total concentration in ground water and drinking water reported here are in the same range as reported in an earlier non-target study (ter Laak et al., 2012). The semi-quantitative total concentration exceeds sum TTCs for genotoxic or endocrine disruptors of 0.01 μg/L (Mons et al., 2013) for all matrices. Thus, adverse effects of the mixture cannot be neglected without more thorough risk assessment.

3.6. Less hydrophobic suspects throughout the water supply chain

The retention time of a chemical is an indicator for its hydrophobicity (Casoni et al., 2009; Bade et al., 2015). The average retention time, weighted for peak intensity, decreases significantly from effluent towards drinking water (Fig. 4, for effluent – surface water – ground water $p < 0.0001$, for ground water – drinking water $p = 0.0418$). This confirms that the more polar chemicals appear in drinking water and hence might be problematic (Wode et al., 2015), as hydrophobic chemicals can be removed more easily from the water phase during environmental loss processes such as sorption and during water treatment. The fact that the REACH legislation by using the PBT criterion encourages to the production of more polar chemicals, has obvious environmental benefits by preventing bioaccumulation and biomagnification of chemicals within the ecological food-chain (Kelly et al., 2004) but at the same time poses challenges to drinking water utilities to remove the more polar chemicals.

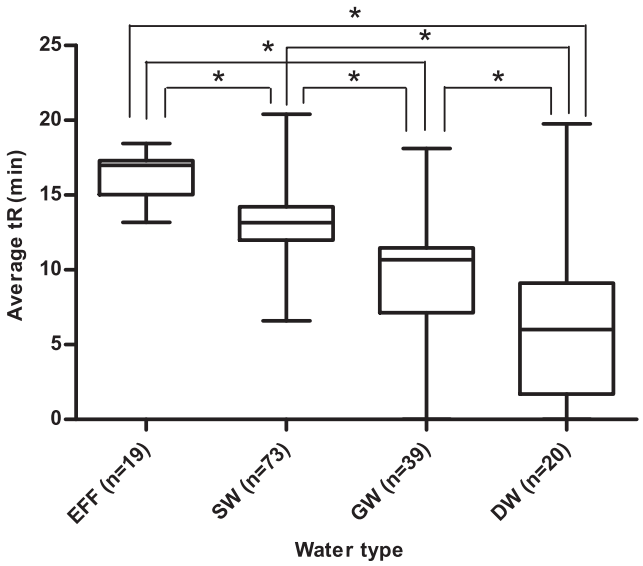

Fig. 4. Average retention time (tR) weighted for peak intensity per water type for detected compounds linked to a suspect detected with a concentration above 0.01 μg/L IS-eq in the positive ionization mode.

4. Discussion

4.1. Comparison to water quality regulations, lists of potentially relevant chemicals and literature data

Of the 44 chemicals on the suspect list that appear in water quality regulations, only one compound is prioritized, the herbicide simazine. Water quality legislations generally focus on well-known chemicals, which are often relatively hydrophobic and almost completely removed during water treatment and environmental processes. Of the potentially relevant chemicals selected by NORMAN and IAWR/RIWA, respectively 6% (37 compounds) and 20% (15 compounds) are prioritized suspects in the current study.

In spite of uncertainties regarding false positives and negatives, this emphasizes the complementarity of the suspect screening LC-HRMS approach compared to the more commonly used target analysis approach.

Of the 174 prioritized suspects in the current study, only 31 chemicals are mentioned in literature based on large target analysis monitoring programs (von der Ohe et al., 2011; Loos et al., 2009, 2013, 2010; Moschet et al., 2014), see Table 6. These are mainly pesticides and partly pharmaceuticals and industrial chemicals. None of the prioritized suspects from the current study are part of the 16 chemicals long JRC watch-list (Carvalho et al., 2015). The

Table 6
Prioritized chemicals in five large monitoring studies that are also prioritized in the current study. The identification confidence level (id. conf. level) according to Schymanski et al. (2014b).

Suspect	id. conf. level	Detected in monitoring studies	Suspect	id. conf. level	Detected in monitoring studies
Pesticides			**Pharmaceuticals**		
caffeine	1	A B C D	irbesartan	4	C
carbofurane	4	E	oxazepam	1	C
chloridazon	1	D E	phenazone	1	D
dimethomorf	1	E	propyphenazone	1	D
fenamidone	4	E	tramadol	1	C
fipronil	4	E	**Industrial chemicals**		
fludioxonil	4	E	benzotriazole	1	A B C
irgarol	4	D E	dibutyl phthalate	4	D
kresoxim methyl	4	E	diisobutyl phthalate	4	D
MCPA	1	B C D E	NPE2C	4	A B D
mecoprop (MCPP)	1	A B C D	N-Acetylaminoantipyrine	1	D
Metolachlor	1	C D	TBP	1	C D
N,N-Diethyltoluamide (DEET)	1	B C D E	TIBP	4	C D
Piperonyl butoxide	4	E	TCPP	1	C D
simazine	1	A B C D E	TCEP	4	C D
Tebuconazole	4	D E			
terbuthylazine	1	A B C D E			

A) Loos et al., 2009, B) Loos et al., 2010, C) Loos et al., 2013 D) Van der Ohe et al., 2011 E) Moschet et al., 2014.

remaining 143 prioritized suspects which have not been described in large monitoring studies could after confirmation of their identity and substance specific risk assessment, be relevant for uptake in monitoring programs.

Only 4 of the prioritized suspects in the current study are detected in available suspect screening studies (Hug et al., 2014; Moschet et al., 2013, 2014; Vergeynst et al., 2014). These compounds are carbofurane, fenamidone, kresoxim methyl (all in Moschet et al., 2013) and TPPO (Hug et al., 2014). The suspects used by Moschet et al. (2013, 2014) for pesticides and by Vergeynst et al. (2014) for pharmaceuticals are for 50–65% comparable to the suspects included in the current study. The current study uses a significant higher number of suspects as well as water samples than suspect screening studies that are published thus far.

4.2. Implications of the method for prioritization results

The prioritization method and the conditions during measuring influence the outcome of the study. The prioritized compounds are the product of the composed suspects list and the performance of the chemical screening method.

The amount of suspects to start with has implications for the amount of retrieved suspects and the trade-off between false positives and false negatives, next to the choice of criteria used (Vergeynst et al., 2015a). A large amount of suspects leads to an increased potential to obtain false positives while a short list of suspects increases the potential to overlook certain chemicals present in drinking water and its sources. Here the approach is to start from a large set of chemicals. Therefore the false positive rate is high: 28% or more (see Section 3.2).

The LC-HRMS non-target screening is used for the detection of a broad range of organic compounds, but the analytical conditions are not optimal for all compounds. Chemicals that could not be isolated with SPE or ionised by ESI will not be detected by this method. The false negative rate is indicated by spiked experiments in drinking water over the last five years. Each analytical series was accompanied with procedure controls including drinking water with 74 reference compounds relevant for surface water quality: 58 in the positive ionisation mode and 16 in the negative ionisation mode at a concentration level of 0.1 μg/L. Around 90% of these reference compounds was recovered: 53 out of 58 compounds in the positive ionisation and 14 out of 16 compounds in the negative ionisation mode. The false negative rate from these experiments is thus about 10% for the set of reference compounds used. The false positive and the false negative rates are both relatively high compared to the detailed study of Vergeynst et al. (2015a) who used a defined set of 77 chemicals and multivariate statistical modelling to optimize this balance.

The absolute response of the 53 reference compounds in the positive ionisation mode shows the effect of isolation recovery and ionisation efficiency (Fig. 5). The response is expressed as the ion counts per ng injected compound. In the positive ionization mode, the response varies within 4 orders of magnitude but for 80% of the standards the variation remains within 2 orders of magnitude. These 53 reference compounds are most likely a good representation of all detected compounds, as they were selected for their relevance for surface water quality.

While the internal standard for negative ionization, bentazone-d_6, has an average response compared to the other reference compounds (Fig. 6), the internal standard for positive ionization, atrazine-d_5, shows relatively high responses (Fig. 5). Therefore the (total) concentrations expressed as in atrazine-d_5 equivalents will generally be underestimated, affecting the number of prioritized suspects at the chosen thresholds. Compounds that are prioritized are likely to have an actual concentration above the TTC-value. In addition, compounds were the actual concentration exceeds the TTC-value may not be prioritized. The TTC is however a very conservative value that can act as a precautionary level for gross of the compounds.

4.3. Possibilities for further improvement of the method

The identity confidence level and quantification of the prioritized suspects needs further improvement by comparing the mass spectrum including MS/MS fragments, the isotopic pattern and the relative retention time and response of a pure reference standard with the suspect compound. Other improvements include more focus on transformation products, the comparison of observed occurrences to modelling results also based on hydrological and land-use characteristics.

As shown the quantity of the detected compounds expressed in IS-eq is not an accurate concentration, due to differences in the isolation recovery (SPE) and the ionization efficiency. Quantification of individual compounds can be improved by (i) using more

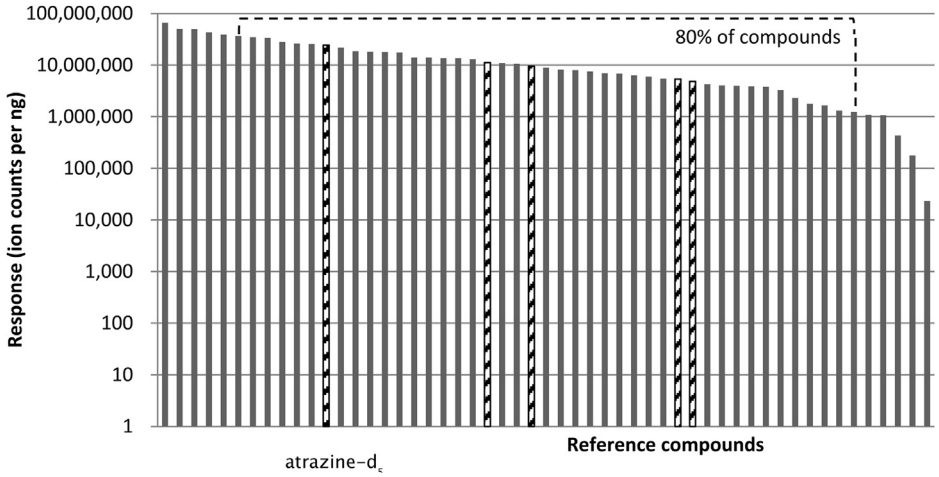

Fig. 5. Response of 53 reference compounds in the positive ionization mode, including atrazine-d_5 and four other internal standards indicated by the striped columns (from left to right: atrazine-d_5, neburon, chloroxuron, 1H-benzotriazole and fenuron).

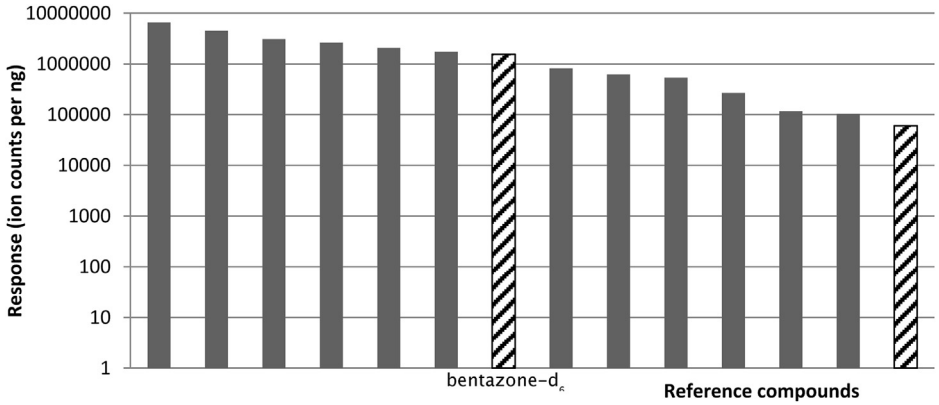

Fig. 6. Response of 14 reference compounds in the negative ionization mode, including betazon-d_6 and one other internal standard chloroxuron, indicated by the striped columns.

internal standards covering a broader range of organic compounds and (ii) using a response factor based on the molecular formula or on specific functional groups.

The current approach only focuses on parent chemicals, which could be broadened to expected transformation products of the chemicals authorized on the European market (Kern et al., 2009; Fenner et al., 2013; Bletsou et al., 2015).

Furthermore, the prioritized compounds can be compared to modelled environmental concentrations for large sets of chemicals (Wambaugh et al., 2013; Judson et al., 2014; Zijp et al., 2014). Coupling of the obtained suspect screening data to water system characteristics, such as hydrology, land-use, treatment technologies involved, or specific susceptible functions of the water system, can further improve our understanding on the occurrence and fate of a wide set of environmentally relevant chemicals.

5. Conclusions

The data-driven approach to prioritize authorized chemicals with suspect screening LC-HRMS data for a wide range of water samples is an important development complementary to currently used target-based approaches. Suspect screening is a relatively fast approach to screen non-target data for the presence of a large set of anthropogenic chemicals. The current approach has the ability to prioritize less well-known compounds, not (yet) included in target-monitoring. This study uses a significant higher number of suspects as well as water samples than suspect screening studies that are published thus far. We prioritized 113 detected compounds linked to 174 suspects, less than 4% of the anthropogenic chemicals present on the European market. A higher number was prioritized for biocides/plant protection products and (veterinary) pharmaceuticals compared to industrial chemicals. The semi-quantitative total concentration decreases and polarity increases along the water cycle; adverse mixture effects cannot be waived.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.watres.2016.02.034.

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