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Prioritizing anthropogenic chemicals in drinking water and sources through combined use of mass spectrometry and ToxCast toxicity data

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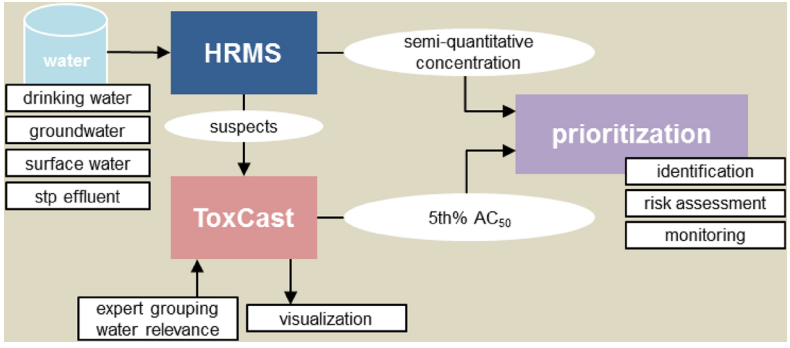
GRAPHICAL ABSTRACT



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ABSTRACT

Advancements in high-resolution mass spectrometry based methods have enabled a shift from pure target analysis to target, suspect and non-target screening analyses to detect chemicals in water samples. The multitude of suspect chemicals thereby detected needs to be prioritized for further identification, prior to health risk assessment and potential inclusion into monitoring programs. Here, we compare prioritization of chemicals in Dutch water samples based on relative intensities only to prioritization including hazard information based on high-throughput *in vitro* toxicity data. Over 1000 suspects detected in sewage treatment plant effluent, surface water, groundwater and drinking water samples were ranked based on their relative intensities. Toxicity data availability and density in the ToxCast database were determined and visualized for these suspects, also in regard to water relevant mechanisms of toxicity. More than 500 suspects could be ranked using occurrence/hazard ratios based on more than 1000 different assay endpoints. The comparison showed that different prioritization strategies resulted in significantly different ranking, with only 2 suspects prioritized based on occurrence among the top 20 in the hazard ranking. We therefore propose a novel scheme that integrates both exposure and hazard data, and efficiently prioritizes which features need to be confidently identified first.

Abbreviations: AC_{50} values, concentrations at half maximal activity; HRMS, high resolution mass spectrometry; ISeq, internal standard equivalent; NTS, non-target screening; TTC, threshold of toxicological concern

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1. Introduction

The ever increasing production and use of chemicals augments their occurrence in drinking water and its sources to an extent that monitoring using targeted chemical analyses alone is no longer sufficient [1–3]. Complementary non-target screening (NTS) methods are required to detect a multitude of chemicals simultaneously [4]. However, identification of all detected chemicals is not yet feasible. Instead, suspect screening based on the matching of a detected peak with the exact molecular mass and also the retention time of a so called suspect chemical in a suspect list or database can be applied [5]. To safeguard drinking water quality, in particular the suspect screening for (emerging) chemicals with potential relevance to human and environmental health has been a key addition to research and policy focusing on target chemicals [6]. Once suspects are detected in environmental samples, they need to be confidently identified [7]. As this is still a labor and time intensive task, suspects need to be prioritized for structural identification prior to risk assessment and potential inclusion in monitoring programs [8,9].

Risks of chemicals are a function of both the exposure to the chemical and its intrinsic hazardous properties. Accordingly, three main strategies are possible for prioritization: a strategy based on exposure – be it modelled or measured, based on hazard, and based on exposure to hazard ratios. In an earlier study the exposure/hazard based strategy was used to prioritize > 1000 suspects detected in 151 water samples including sewage treatment plant effluent, surface water, groundwater and drinking water using relative intensities [5]. These suspects had been tentatively identified through matching against a curated suspect list of > 5000 water relevant chemicals. The suspects were prioritized when their exposure levels exceeded water type specific prioritization thresholds based on the threshold of toxicological concern (TTC) [10,11] corrected for dilution and removal during the water cycle. These generic thresholds conservatively represented exposure levels at which health risks were unlikely.

Alternatively, chemical-specific toxicity information of suspects can be used. Databases comprising detailed health risk assessments such as the International Toxicity Estimates for Risk (ITER) database which includes information from the WHO International Programme on Chemical Safety (IPCS), the U.S. EPA, the Agency for Toxic Substances and Disease Registry (ATSDR), Health Canada, IARC, and RIVM, or other sources such as European Food Safety Authority (EFSA), European Medicines Agency (EMA) and the U.S. EPA Integrated Risk Information System can be searched chemical-by-chemical for established acceptable daily intake levels. Also, *in vivo* toxicity databases such as the TOXNET databases from the US National Institute of Health (NIH) or the databases provided by the European Chemical Agency (ECHA) can be consulted. However, for many emerging chemicals sufficient toxicity data are lacking [12]. To efficiently prioritize the multitude of candidates generated by suspect screenings, toxicity databases allowing automated approaches and including information on many emerging chemicals are needed. The U.S. EPA's ToxCast database is a publicly available database in which high throughput *in vitro* toxicity information is collected for over 8000 different environmentally relevant chemicals and over 1000 biological endpoints [13,14].

Despite current developments in physiology based kinetic modelling to calculate oral intake associated with effective *in vitro* concentrations [15–17], it is still challenging to use *in vitro* toxicity data for human health risk assessment. However, the use of *in vitro* toxicity data to compare the hazardous properties of chemicals in prioritization approaches is less disputed, in particular as cellular and molecular response are the critical initiators of adverse health and population effects [18]. For instance, Rager et al. used ToxCast data to prioritize suspect chemicals in house dust [19], and Blackwell et al. prioritized relatively well-known target chemicals in surface water through a combination of chemical occurrence and toxicity data based on calculated exposure - activity ratios [20].

Here, we extend this integrated prioritization strategy to other water matrices and a broader set of water relevant suspect chemicals, thus advancing its application on target chemicals to suspects detected in an NTS dataset [5]. We expand the previous prioritization by Sjerps et al., and compare it to a prioritization using chemical-specific exposure/hazard ratios. To this end, we first assess and visualize ToxCast data availability and density for the detected suspects, also in regards to water relevant mechanisms of toxicity. We then rank suspects based on their concentrations at half maximal activity (AC_{50} values), and compare the differences in prioritized chemicals between the two strategies. Ultimately, a synergistic prioritization workflow is presented that efficiently ranks suspect chemicals detected in NTS analyses, enabling subsequent confirmation of the suspects' identity and ultimately inclusion into monitoring programs and regulation.

2. Experimental

2.1. Exposure data

The suspect candidates presented in this study are based on the HRMS non-target screening data described in [5]. In brief, this data set consisted of 151 Dutch water samples including waste water effluent (19), surface water (73), ground water (39) and drinking water (20) collected as described by Hogenboom et al. [21] in the period 2007-2014. Following LC-HRMS analysis, a suspect screening was performed against an in-house curated suspect list of anthropogenic chemicals authorized on the market via various European regulatory frameworks (SI Table 1, sheet SI Sjerps 2016 suspect list). 1461 suspects corresponded to 927 features detected in positive (1037 suspects from 619 features) and negative (424 suspects from 308 features) ionization mode (SI Fig. 1). Suspect concentrations were expressed as internal standard equivalents (ISeq) of atrazine-d5 or bentazone-d6 equivalents in the positive or negative ionization mode, respectively. ISeq were used to prioritize suspects detected in the different water matrices based on thresholds derived from the most conservative TTC for chemicals in drinking water, expected generic drinking water treatment efficiencies and expected generic dilution within the water cycle; 1.0 mg/L ISeq for effluent, 0.1 mg/L ISeq for surface water and 0.01 mg/L ISeq for ground-and drinking water. To allow for comparison between exposure and toxicity based prioritization approaches, suspects were also ranked based on their exposure according to water type. The full list of suspects and ISeq is provided in SI Table 1, sheet ``SI suspect prioritization". Suspects prioritized based on their exposure are listed in bold.

2.2. Toxicity data

AC_{50} values in uM were retrieved for all active and tested chemical-assay combinations from the U.S. EPA's online ToxCast data repository (https://doi.org/10.23645/epacomptox.6062479.v1, provided in the INVITRODB_V2_SUMMARY files oldstyle_ ac50_Matrix_151020.csv and Chemical_Summary_151020.csv), including information on the number of assays in which a chemical was tested, and the number of assays in which a positive response was observed, In this file, inactive and tested chemical-assay combinations were represented by 10e6, not tested by NA. The ToxCast assay endpoint coverage of relevant toxicity mechanisms for water-relevant chemicals described previously was evaluated based on ToxCast annotations [22,23]. Water-relevant endpoints were related to xenobiotic metabolism, modulation of hormone systems, reactivity, stress response, reproduction and development. Additional water relevant endpoints included general cell viability, thyroid toxicity, neurotoxicity, and PPAR receptor activation [24–26]. The full list of assay endpoints and assigned mechanisms can be found in SI Table 1, sheet "SI water-relevant mechanisms". To evaluate the data availability for prioritization, AC_{50} values of detected suspect chemicals

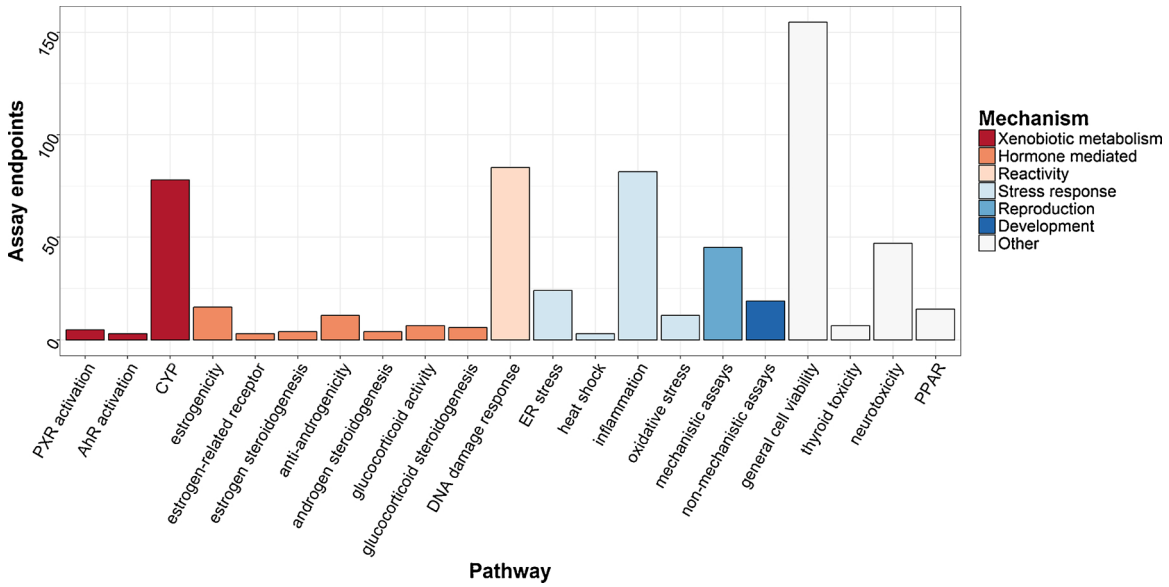

Fig. 1. Presence of water relevant mechanisms and related pathways in ToxCast database.

were extracted from the ToxCast database using their CAS numbers as chemical identifiers. Retrieved ToxCast data is included in SI Table 1, sheet "SI suspect prioritization". For 788 CAS numbers there was no match in ToxCast, which could be due to faulty CAS numbers and/or lack of ToxCast data of a given chemical. These contain NA values in SI Table 1. For all available ToxCast assay endpoints in a hypothesis free approach and for water-relevant mechanisms, ToxCast data availability was evaluated and AC_{50} values were visualized in heat maps. AC_{50} values of previously prioritized suspects based on their relative intensities and water type were compared to those of non-prioritized suspects with a Student's *t*-test. Data handling and visualization were performed in R version 3.4.1. R-scripts in R markdown format and the input files with the CAS numbers of the suspects detected in Sjerps et al. (Sjerps_suspects_CAS.csv) and the water relevant assay endpoints (toxcast_waterRelevant.csv) are provided in the SI.

2.3. Priority score

The 5th percentile rather than the minimum AC_{50} values was used to reduce the potentially disproportionate impact of sensitive assay endpoints. The relative intensities of suspect chemicals were combined with ToxCast toxicity information to calculate a synergistic priority score by dividing the ISeq corrected for the water type by the 5^{th} percentile AC_{50} values. Priority scores are included in SI Table 1, sheet "SI suspect prioritization".

3. Results & discussion

3.1. ToxCast data availability for suspect chemicals detected in drinking water and its sources

The US EPA's ToxCast database provides high throughput *in vitro* toxicity information on more than 8000 environmentally relevant chemicals for more than 1000 biological endpoints, covering a wide range of biological processes [14,27]. To evaluate the aptitude of the ToxCast database for prioritization of suspect chemicals detected in water samples assay endpoints were screened for mechanisms previously described as water relevant, related to xenobiotic metabolism, modulation of hormone systems, reactivity and adaptive stress responses [22,23]. Both endocrine disruption and DNA reactivity may underlie carcinogenesis and be related to reproduction, developmental effects, and health effects with considerable impact on quality of life [24]. Additional water relevant endpoints include neurotoxicity [25] and PPAR receptor activation [26]. The list of mechanisms and their respective assay endpoints can be found in SI Table 1. In total, 631 ToxCast assay endpoints from a total of 21 pathways were related to the water relevant mechanisms, illustrated in Fig. 1. As emerging chemicals might be associated with alternative mechanisms-of-action, conservatively all available ToxCast assays were included in the following.

For roughly half of the 1461 suspects detected in Dutch water samples (673) toxicity data was included in ToxCast. The number of assays in which a chemical was tested varied widely; on average, a chemical was tested in 443 distinct assay endpoints (range: 45–1090; median: 337). ToxCast data density for suspects in regards to water relevant mechanism is illustrated in Fig. 2. 418 suspects were tested in water-relevant assays. None of these assay endpoints covered the categories "Reproduction" and "Development".

A heat map further illustrates the density of all ToxCast data for the suspect chemicals and their toxicity (see SI Fig. 2 for a zoom-in of this heat map), showing significant differences between the suspect chemicals' activity and indicating that a prioritization based on toxicity can be effective. The chemicals with the largest number of observed responses and with the highest toxicity i.e. lowest $AC_{50,}$ included plant protection chemicals and industrial chemicals (SI Table 1). The assay endpoints for which the lowest AC_{50} values were reported related to p53 activation, the PPAR receptor, estrogen receptor alpha and the thyroid hormone receptor representing the earlier defined water relevant mechanisms and pathways (Fig. 1).

3.2. Comparison of prioritization based on exposure and toxicity

Next, it was evaluated whether the toxicity based prioritization of suspect chemicals corresponded to the exposure based ranking. To reduce the disproportionate impact of sensitive assay endpoints, the 5th percentile of AC_{50} values was used as a measure of toxicity for a given suspect instead of its minimum AC_{50} value. 5th percentile AC_{50} values of the suspects that had been prioritized earlier according to their semi-quantitative concentrations and water type were compared to non-prioritized suspects. The median 5th percentile AC_{50} of all exposure based prioritized suspects was significantly higher (p-value < 0.05) in the positive ionization mode, and significantly lower for chemicals detected in negative ionization mode (Fig. 3). 5th percentile AC_{50} toxicities of prioritized and non-prioritized suspect chemicals based on semi-quantitative exposure levels spanned the same 7–8 orders of

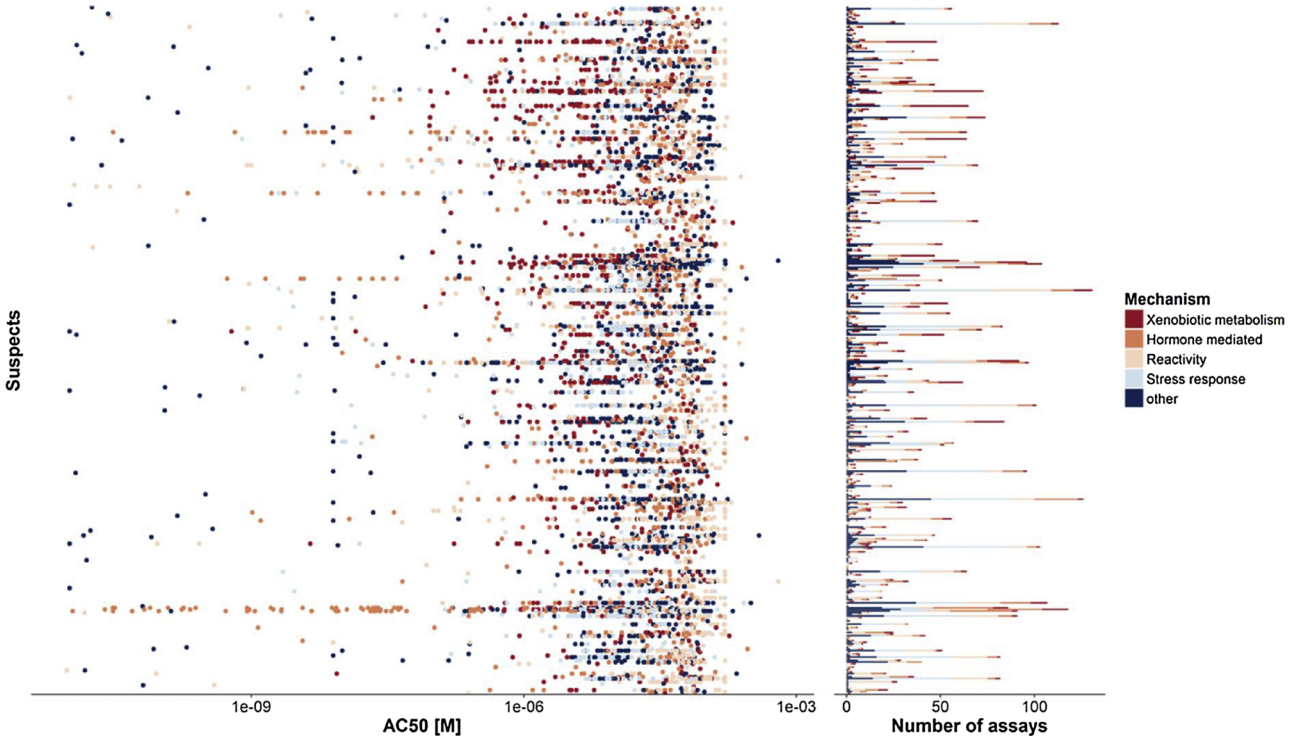

Fig. 2. AC_{50} values from water relevant ToxCast assay endpoints for detected suspect chemicals (left), and number of assays per mechanism (right) are shown.

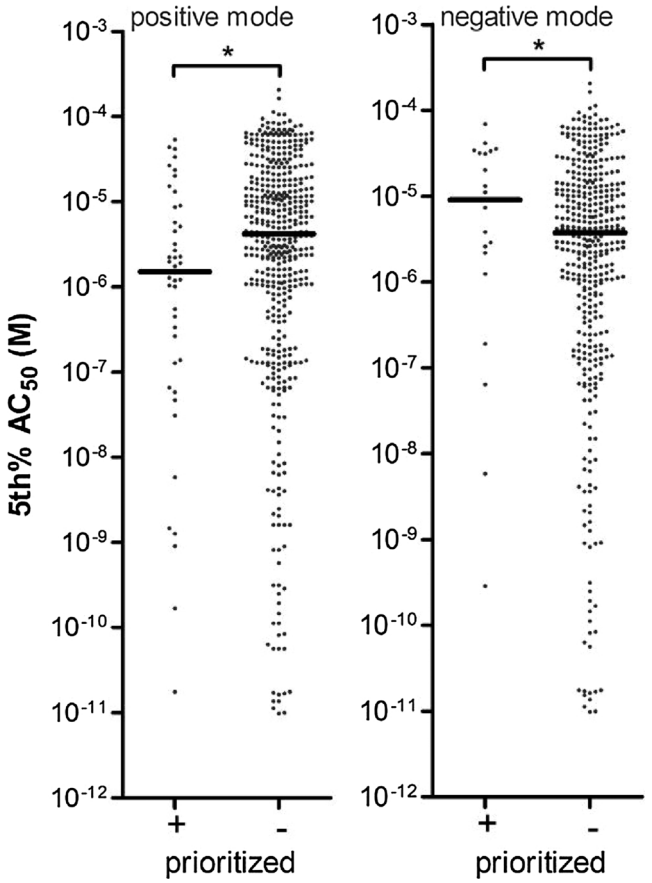

Fig. 3. Comparison of toxicity (5th percentile AC_{50} values) of suspects prioritized (+) or not (-) based on their semi-quantitative concentrations, detected in positive (left) or negative (right) ionization mode. Dots represent individual 5th percentile AC_{50} values, bars indicate the median.

magnitude, ranging from mM to sub-nM. This indicates that relevant hazardous chemicals could be missed when prioritizing solely on semi-quantitative exposure levels and generic toxicity thresholds.

Fig. 4 depicts the 5th percentile AC_{50} values and the ISeq of the respective suspects, distinguishing classes of suspect chemicals ranging from the combination of high toxicity and high exposure, to the combination of low toxicity and low exposure. Over 20 suspect chemicals exhibited high toxicity, i.e. 5th percentile AC_{50} values in the sub-nanomolar range (SI Table 2). Only 4 of these chemicals were prioritized based on exposure, emphasizing the complementarity of the two prioritization strategies.

A synergistic priority score seemed optimal to address this complementarity, where semi-quantitative exposure levels in water would be divided by the 5th percentile AC_{50} values, comparable to the exposure − activity ratios described by Blackwell et al. [20]. The cumulative distribution of these priority scores (ratio of ISeq occurrence/5th % AC_{50}) is illustrated in SI Fig. 3. It shows that the priority scores of sewage treatment plant effluent and surface water are roughly 100x and 10x higher, respectively, than those of groundwater and drinking water. When the semi-quantitative exposure levels in surface water and effluent were corrected for the expected dilution in the water cycle and drinking water treatment efficiencies, i.e. scores were divided by 10 and 100, this generated a priority score across water types ranging from 10^{-7} to 10^{4} for all water types in both positive and negative ionization mode (SI Fig. 3).

3.3. Prioritized chemicals differ across prioritization strategies and water types

Per suspect chemical, calculated priority scores corrected for water type were ranked (SI Table 1, sheet “SI suspect prioritization”). Ranking based on priority in drinking water is shown in Table 1. Only 2 of the highly ranked suspect chemicals, i.e. UT-637 and vinyltoluene, had been prioritized based on occurrence only [5].

The identity of the prioritized suspects should now be confirmed, starting with methyl benzoate, used as a solvent and fragrance with a

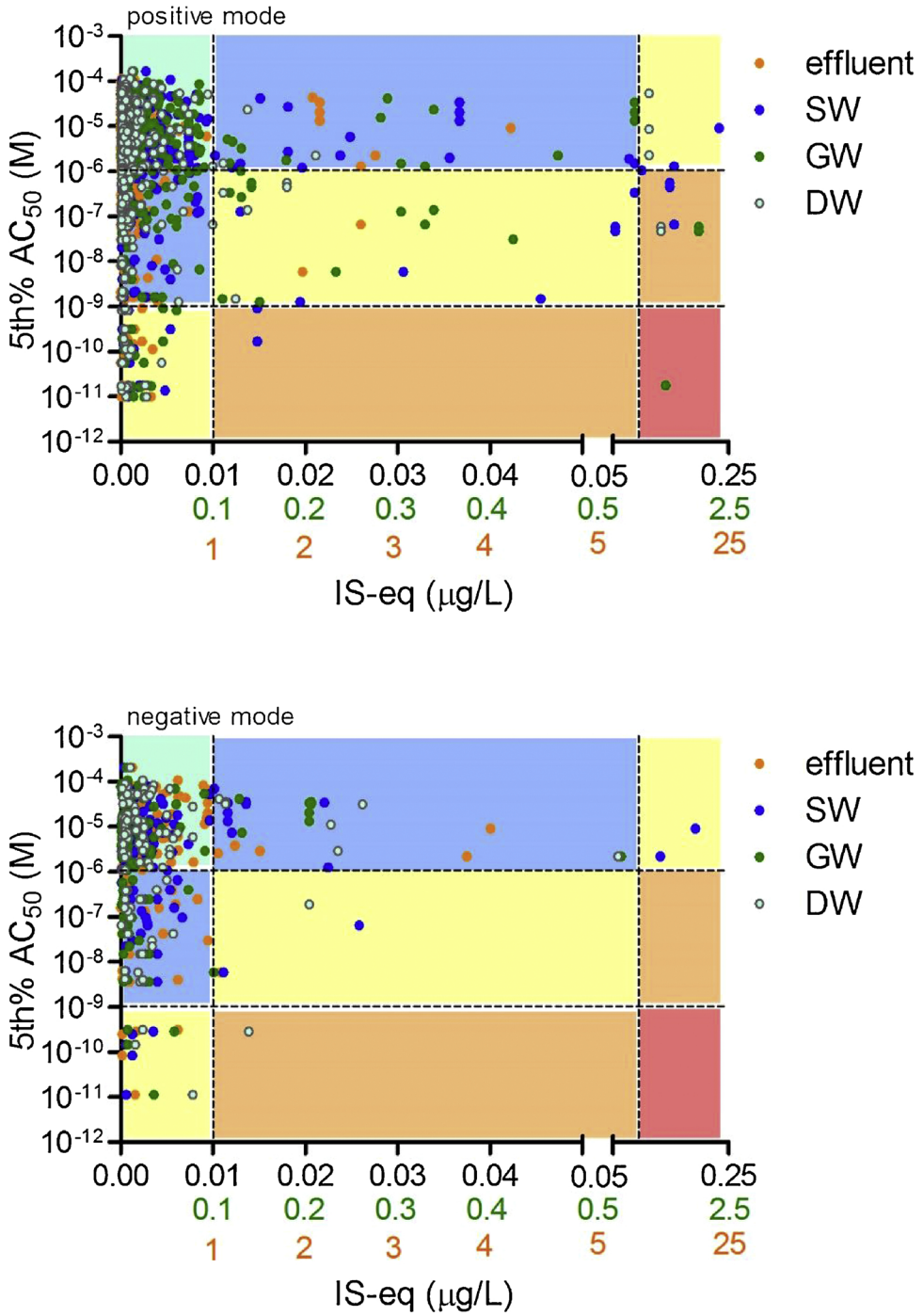

Fig. 4. Suspects detected in sewage treatment plant effluent (orange dots), surface water (SW, blue dots), groundwater (GW, green dots) and drinking water (DW, white dots) are plotted according to their toxicity (5th percentile AC_{50}) and exposure (ISeq, black data for GW/DW, green for SW, orange for effluent). The vertical dashed lines indicate the exposure threshold and 10x the threshold, the horizontal lines divide the 5th percentile values into three arbitrary potency classes of toxicity. Suspects detected in positive and negative ionization mode, respectively, are shown in the upper and lower panel.

phenolic type odor (CAS: 93-58-3), 1-ethyl-2-pyrrolidinone, used as a fragrance and in protein research (CAS: 2687-91-4), and 2,4,4-trimethylpentene, used as a chemical intermediate for paints, lacquers and varnishes (CAS: 25167-70-8) [28]. These chemicals are all included in the REACH Registry List of chemicals (echa.europa.eu) with a production volume of > 100 ton per year in the case of methyl benzoate, and > 1000 ton/year for 1-ethyl-2-pyrrolidinone, and 2,4,4-trimethylpentene. 2,4,4-Trimethylpentene is also listed on ECHA's Candidate List of substances of very high concern for Authorization (iPBT list) as candidate chemical that needs to be evaluated for its persistence, bioaccumulation, and toxicity properties.

Standardization of prioritization schemes for the results of non-targeted screening approaches may be needed to obtain a legislative basis for non-target screening methods for water quality regulations such as the EU Water Framework Directive including the Groundwater Directive and the Drinking Water Directive [3,29,30]. The prioritization strategies developed here can be useful for the risk-based monitoring framework as demanded by the EU Drinking Water Directive (Annex II), which requests to repeatedly evaluate which individual chemicals to include in monitoring efforts [31]. Following confirmation of these

Table 1
Highest ranked suspect chemicals based on drinking water priority scores corrected for water type. DW drinking water, GW groundwater, SW surface water. * indicates corrected for water type, i.e. divided by 10 for surface water, and 100 for effluent.

Suspect name	Ion. mode	Exposure priority	ToxCast assays (active / total)	min AC_{50} [M]	5% AC_{50} [M]	Mechanism with lowest AC_{50}	DW	GW	SW*	effluent*
Methyl benzoate	-	no	3 / 339	1.1E-11	1.1E-11	Reactivity	689	318	53	138
1-Ethyl-2-pyrrolidinone	+	no	3 / 279	9.3E-12	9.8E-12	Reactivity	284	258	76	8
2,4,4-Trimethylpentene	+	no	1 / 113	1.8E-11	1.8E-11	other	150	162	136	5
Diethyl oxalate	+	no	4 / 339	4.4E-11	5.7E-11	other	79	45	10	1
2-Ethylhexyl cyanoacetate	+	no	1 / 113	1.0E-11	1.0E-11	general cell viability	55	141	58	326
2,6,6-Trimethyl-2-cyclohexene-1,4-dione	+	no	1 / 113	1.7E-11	1.7E-11	general cell viability	50	73	71	27
UT-632	**-**	**yes**	**11 / 337**	**2.7E-11**	**2.9E-10**	**general cell viability**	**48**	**20**	**12**	**6**
Vinyltoluene	**+**	**yes**	**1 / 113**	**1.8E-11**	**1.8E-11**	**general cell viability**	**46**	**8038**	**114**	**8**
Prop-2-en-1-yl 3-cyclohexylpropanoate	+	no	3 / 279	1.0E-11	1.6E-11	Reactivity	36	131	119	122
tert-Butyl acrylate	+	no	1 / 113	1.4E-11	1.4E-11	general cell viability	11	30	352	75
Glycidyl methacrylate	-	no	5 / 339	1.8E-11	1.5E-10	Reactivity	11	5	4	4
(5-Ethyl-1,3-dioxan-5-yl)methanol	+	no	3 / 113	6.5E-11	8.2E-11	general cell viability	11	19	13	5
Camphor	+	no	1 / 113	1.1E-10	1.1E-10	general cell viability	10	3	3	7

suspects through structural identification based on fragmentation spectra and/or reference standards, the health risk of confirmed suspects needs to be assessed in more detail based on available *in vivo* toxicity data, *in vitro/in vivo* extrapolation and QSAR and read-across approaches. When indeed confirmed as relevant, introduction of the chemical in routine monitoring programs and/or risk management measures might follow.

3.4. Future perspectives

The presented integrated prioritization does not impart relative weights to the parameters representing exposure and toxicity. However, mass spectrometry is not inherently quantitative and differences in ionisation efficiency can lead to relative intensities of compounds not accurately reflecting their concentrations [5,32]. As illustrated in SI Fig. 4, if a 10-fold deviation in signal is considered, the top 10 ranked suspects detected in drinking water will still remain in the top 40 even if their actual concentration is 10x lower. Nevertheless, it might be beneficial to attribute less weight to the relative intensities than to the AC_{50} value in a weighted final prioritization score and/or also exploit the frequency with which a suspect is detected, as well as a change in its intensity through water treatment steps. Besides, the number of active assay endpoints could further refine prioritization. For instance, both Rager et al. and Newton et al. prioritized suspects in house dust and U.S. drinking water, respectively, based on estimated exposure and detection frequency data from HRMS analyses, in combination with ToxCast toxicity data, and modelled exposure data using US-EPA's ExpoCast Software [19,33]. In their model, relative intensities receive lower weight than detection frequency.

Here, the 5th percentile of AC_{50} values was used as a measure of toxicity, in analogy with the 5th percentile in a species-sensitivity distribution for ecotoxicological risk assessment and the 5th percentile of NOELs to derive TTC values [10,32]. It needs to be further evaluated whether prioritization changes when other parameters for toxicity are used, for example the lowest observed AC_{50} or the median AC_{50}. As relevant effects can be observed at lower concentrations, a point-of-departure strategy, eg signal-to-noise or LOEC (lowest observed effect concentration) instead of AC_{50} values could also be evaluated [33]. For approximately half of the suspects detected in Dutch water, ToxCast data were absent. For these, toxicological information may be available in other databases and literature, alternatively predictive *in silico* tools can be used to estimate toxic properties [34–36]. The dependency of this method on ToxCast data availability, as well as the requirement of an initial match to a suspect in a suspect list or compound database are limitations of the presented method. In particular, transformation products, although a highly relevant issue for drinking water safety, are rarely covered by either of them and will continue to require strategies alternative to the one presented here. However, with the increase of compounds in suspect lists and databases – for instance the NORMAN SusDat database increased from 14′000 to over 40′000 entries in the last year – and the on-going efforts of the US EPA to add more compounds and assay endpoints to ToxCast, we envision that the strategy

presented here has and will become even more useful. Moreover, with the very recently released integration of ToxCast into the identification software MetFrag, we predict that this strategy will become a routine prioritization method in the future.

Finally, it has to be emphasized that ToxCast *in vitro* hazard data are no replacement for health risk assessment as they are not per definition correlated to acceptable daily intakes for humans. Accordingly, a comparison of health-based reference values for oral exposure collected from ECHA registration dossiers for the suspect chemicals with the 22 lowest and the 25 highest AC50 values in ToxCast, respectively, showed no significant difference (SI Figure 5). While the use of *in vitro* hazard data in prediction of potential adverse health effects in humans is limited, its integration in prioritization strategies is highly useful and efficient, as presented here for the prioritization of suspects detected in Dutch drinking water and sources.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jhazmat.2018.10.044.

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