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Computational material flow analysis for thousands of chemicals of emerging concern in European waters

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GRAPHICAL ABSTRACT
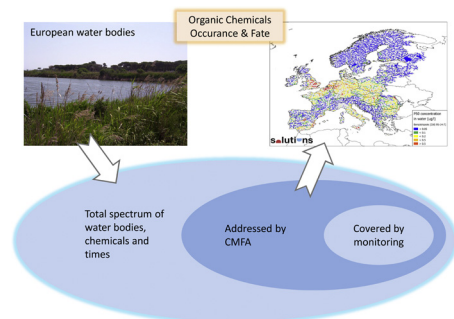
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ABSTRACT

Knowledge of exposure to a wide range of chemicals, and the spatio-temporal variability thereof, is urgently needed in the context of protecting and restoring aquatic ecosystems. This paper discusses a computational material flow analysis to predict the occurrence of thousands of man-made organic chemicals on a European scale, based on a novel temporally and spatially resolved modelling framework. The goal was to increase understanding of pressures by emerging chemicals and to complement surface water monitoring data. The

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Emissions
Fate and transport

ambition was to provide a first step towards a "real-life" mixture exposure situation accounting for as many chemicals as possible. Comparison of simulated concentrations and chemical monitoring data for 226 substance/basin combinations showed that the simulated concentrations were accurate on average. For 65% and 90% of substance/basin combinations the error was within one and two orders of magnitude respectively. An analysis of the relative importance of uncertainties revealed that inaccuracies in use volume or use type information contributed most to the error for individual substances. To resolve this, we suggest better registration of use types of industrial chemicals, investigation of presence/absence of industrial chemicals in wastewater and runoff samples and more scientific information exchange.

1. Introduction

Over 350,000 chemicals and mixtures of chemicals have been registered for production and use (Wang et al., 2020). As a result of their use, many of these chemicals find their way to European freshwater systems (Stroomberg et al., 2018; Liška et al., 2015; Schulze et al., 2019) and coastal waters (UNESCO and HELCOM, 2017). The EU Water Framework Directive (WFD) requests water managers to establish the likelihood that any of these chemicals or their mixtures negatively affect the ecological status of surface waters and ground waters or affect the drinking water production. When and where necessary, measures should be taken to remediate this (EEA, 2018).

Water quality characterization is primarily done by surface water sampling and chemical analysis, focusing on up to several hundreds of individual priority substances and river basin specific substances at most. This inevitably provides an incomplete picture: the number of stations, samples and analysed chemicals is limited, and measurement accuracy may be hampered by limits of quantification. This limits the possibilities to effectively manage chemicals in aquatic ecosystems (Nilsen et al., 2019). Model-based approaches may complement monitoring by filling these information gaps (Brack et al., 2017). Moreover,

modelling can reveal probable causal links between socio-economic drivers of the use of chemicals (population density, land use, standard of living, management practices), via the subsequent pressures by emissions of chemicals to the environment, the resulting chemical status expressed by the concentrations of chemical mixtures and the impact on ecosystems and human health. Such causal links provide predictive power to evaluate the expected benefits of management responses and may address future changes in emissions of chemicals due to developments in society and economy.

The use of spatially and temporally explicit water quality models on the global or continental scale is not new (Kroeze et al., 2016), and would add key information to exposure models used in chemical safety assessment contexts, which typically neglect spatio-temporal variability (e.g. EUSES; https://ec.europa.eu/jrc/en/scientific-tool/european-union-system-evaluation-substances). Applications of spatially and temporally explicit models to emerging contaminants are currently limited to a restricted number of chemicals and/or a restricted spatial domain. The quantification of emissions is provided by various methods, e.g. by WWTP pathway modelling (Oldenkamp et al., 2018; Kapo et al., 2016; Kehrein et al., 2015; Ferrer and DeLeo, 2017), by modelling of the terrestrial run-off and erosion pathway (Nizzetto et al.,
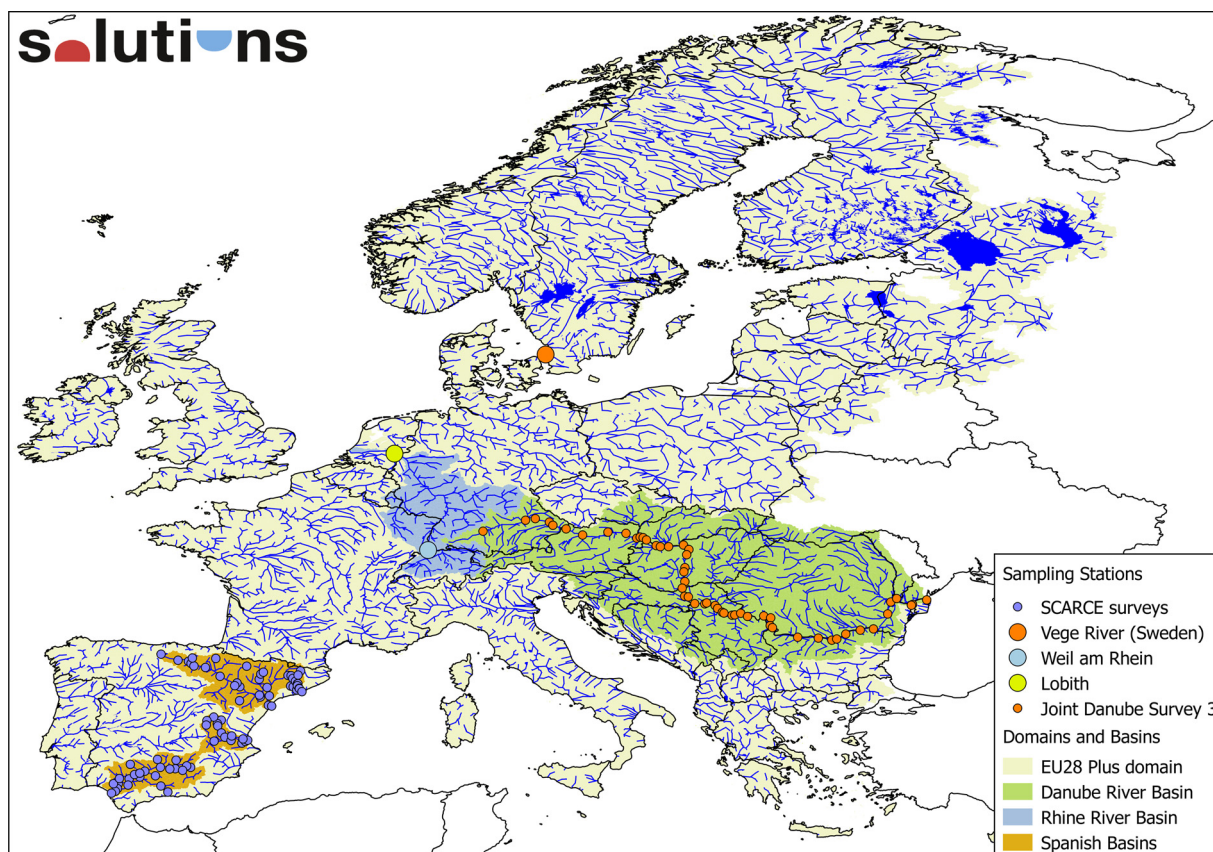

Fig. 1. Europe-wide spatial domain (EU28 Plus) and CMFA evaluation case study basins (Rhine, Danube and four Spanish Basins Ebro, Guadalquivir, Júcar and Llobregat) and sampling stations. Stations with time series data are shown by large symbols; stations in survey data sets are shown by small symbols.

2016; Pullan et al., 2016) or by inverse modelling (Pistocchi et al., 2019). None of these models address hundreds or thousands of chemicals on a continental scale. Consequently, none of them can support European water managers sufficiently in answering the question to what extent the full plethora of man-made chemicals is likely to negatively affect the ecological status of surface waters and ground waters, or the drinking water production.

In this paper we explore what model-based approaches can achieve to address the information gap outlined above, with the aim to prepare for taking action (Funk and Ash, 2020). The key challenge is to deal with the high number of chemicals. This demands that the techniques and data sources used can be applied to a wide spectrum of chemicals with an acceptable effort. Dedicated site-specific data collection and substance-by-substance manual model calibration need to be avoided. Many of the abovementioned existing model applications for emerging chemicals demonstrate that the accuracy of such model is high, if data of sufficient quality are collected and models are carefully calibrated. We will evaluate their accuracy when such efforts are no longer affordable due to the large amount of chemicals involved, by comparing estimated water concentrations to measured water concentrations for as many chemicals as possible in selected river basins across Europe. As model accuracy is expected to be reduced, we will analyse to what extent the results are still useful to assist EU water managers while dealing with chemicals. Various sensitivity tests were made to understand the critical factors limiting model accuracy, and to understand what needs to be done to improve the results for better support to EU water management.

As our approach differs from commonly used modelling, we will refer to it as Computational Material Flow Analysis (CMFA). It addresses the emissions, transport and fate for as many organic chemicals as practically possible. We extend currently available tools to state-of-the-art spatio-temporal modelling. The results are intended for the subsequent assessment of environmental (Posthuma et al., 2019) and human health mixture risks (Kortenkamp et al., 2018), and will thus support water managers with insights necessary to formulate cost-effective responses to prevent and mitigate the risks from chemicals.

2. Materials and methods

2.1. Computational material flow analysis

The CMFA follows a two-step approach: (i) the simulation of emissions, and (ii) the simulation of fate & transport. The spatial schematisation as well as the hydrology and temperature forcing, soil type, land use and crop cover were derived from the Europe-wide hydrology model E-Hype (Hundecha et al., 2016). The E-Hype subcatchments (SC) provide an irregular horizontal subdivision of the spatial domain, with an average size of 252 km^2. Fig. 1 shows the spatial domain and river network, as well as the basins and sampling stations for CMFA evaluation. In order to make the CMFA suitable for application to large numbers of chemicals and to yet un-investigated chemicals of emerging concern, the CMFA does not to rely on detailed site-specific input data and substance-by-substance manual model calibration.

The estimation of emissions to surface waters and soils was based on a "source oriented" approach (European Commission, 2012). The first step was the quantification of the releases of chemicals to surface waters, wastewaters and soils prior to stormwater and wastewater management. This is referred to as "losses" (see also Fig. 2). We first estimated the losses to surface waters, wastewaters and soils, per country or for Europe. Next, these losses were distributed in space and time, and the wastewater and storm water management pathways were quantified. This yielded estimated time- and space-dependent emissions to surface water and soils. We distinguished two groups of substances with one specific use type, plant protection products (PPPs) and pharmaceuticals, and one group of "REACH registered" substances with

multiple use types. See S1 for complete formulations and input data used.

2.1.1. Chemicals losses to wastewater, surface water and soils

The losses of pharmaceuticals were estimated based on public per-capita sales data from Sweden (about 800 substances, Socialstyrelsen, 2015), the United Kingdom (about 1000 substances, Boxall et al., 2012), Austria, Switzerland, France, Luxembourg and the Netherlands (4 substances; IKSR, 2009). Human excretion was assumed to be 12% of the amount sold for all pharmaceuticals. This is the consumption weighed average of the excretion reported for 56 pharmaceuticals by Lindim et al. (2016c). All losses were assumed to reach the wastewater. The losses of active ingredients of PPPs to air, surface water and soil have been estimated by Sala et al. (2015) for 22 EU countries, based on the harvested area approach: prescribed crop- and substance dependent application rates were combined with known agricultural land uses. For REACH registered chemicals, the losses were estimated based on registered amounts produced, imported and exported (so-called EU tonnages) from the REACH registration dossiers. Losses to air (8.5%), water (12%) and soil (3.0%) were estimated from loss factors for various use categories and life cycle stages (specific Environmental Release Categories or spERCs; CEFIC, 2012). Information to link all individual chemicals to specific use categories and the associated spERCs was lacking. Consequently, the same estimated loss fractions had to be used for all REACH registered chemicals. Both the group of PPPs and the group of REACH registered chemicals contained substances registered under the Biocidal Products Regulation (BPR, Regulation (EU) 528/2012). Thus, we will denote the group of PPPs as "pesticides" in the remainder of this paper.

2.1.2. Spatial distribution

The losses to the environment and to wastewater were spatially distributed following "locator" values. For REACH-registered chemicals and pharmaceuticals, the locator was *Pop x GDP-PPP x WF,* where *Pop* indicates the population (cap) and *GDP-PPP* represents the gross domestic product based on purchasing-power-parity (USD/cap). This number quantifies standard of living, and we assumed that a higher standard of living implies a higher use of chemicals. *WF* is a unitless factor to account for a relative reduction of the losses with increasing standard of living due to increasing effectiveness of environmental management varying between 1.0 (no management) and 0.5 (best management) (S1). To quantify this effect in relation to standard of living, we used existing wastewater management practices as an indicator. The value of 0.5, or 50% emission reduction at optimal environmental management, was based on expert judgement. For pesticides, we used agriculture land use as defined in the hydrological model as the locator. The emissions were further distributed in time, assuming
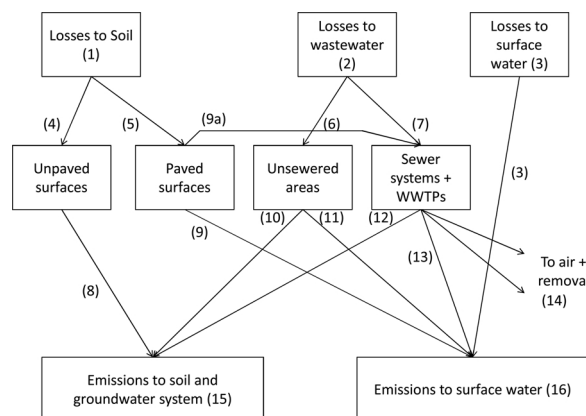

Fig. 2. Schematic overview of fluxes in the emission estimates (numbers refer to Table 2).

7-day application periods randomly distributed during the relevant season of cultivation (spring crops, autumn crops and perennial crops).

2.1.3. Wastewater and storm water pathways

The emissions to impermeable surfaces accumulate there, until they are washed off. Wash-off was assumed to start at 2 mm/day of rainfall and to be complete at 5 mm/day. This represents a linearized approximation of commonly used exponential relationships (Huber, 1986; see S1). The washed off chemicals proceed to wastewater treatment plants (combined sewers) or to surface waters (separated sewers). Wastewater is either collected by sewer systems or disposed of locally. The latter fraction is partly directed to surface waters and the remainder to soils. The fate of the collected wastewater was classified as untreated, primary treated, secondary treated or higher level treated. Based on simulations with SimpleTreat (Struijs, 2014), the fate of every individual chemical in an activated sludge treatment plant was calculated. The SimpleTreat results were directly applied to the secondary or higher order treated share of collected wastewater. The untreated share of collected wastewater is directly discharged to surface water. For the primary treated share of collected wastewater, the fraction to sludge calculated by SimpleTreat was applied and the remaining fraction of the chemical was supposed to remain in the effluent. The fraction to sludge was either removed from the simulation, if the sludge is incinerated or isolated in landfills, or discharged to soils.

2.1.4. Fate and transport

For the chemicals' fate and transport we used a dynamic mass balance model that calculates contaminant concentrations in a spatially and temporally resolved way. The model has been coupled with the Delft3D-WAQ open source modelling framework (http://oss.deltares. nl/) and is called STREAM-EU (Spatially and Temporally Resolved Exposure Assessment Model for European basins; Lindim et al., 2016a, 2017). STREAM-EU includes state-of-the-art formulations for partitioning, degradation, volatilization, precipitation/dissolution, ionization and losses to aquatic sediments. See S2 for complete mathematical formulations. The Delft3D-WAQ framework was used to generate mass balances, which we used to check model consistency and to designate material flows.

2.1.5. Substance properties

Substance properties were derived from substance structure property models. See S3 for an overview of required parameters, substance structure property models used and data gap handling in cases where not all required substance parameters could be provided by models.

2.2. CMFA application and evaluation

Computations were carried out for Europe as a whole (Fig. 1). For CMFA evaluation by comparison of predicted and measured concentrations, field datasets were collected that satisfy the following conditions: (a) cover conditions across Europe; (b) cover as many chemicals as possible; (c) mention if analyses results are affected by limits of detection and quantification; (d) be homogeneous with respect to methods for sampling, analysis and quality control; (e) offer coverage in the spatial domain (survey covering many stations) or temporal domain (long time series). Table 1 provides an overview of the datasets used. The sampling locations of the selected datasets are shown in Fig. 1.

CAS numbers were used for substance identification. From all datasets, chemicals that were not analysed at a significant number of stations (SCARCE, JDS3) or with a much lower data frequency (RIWA-Rijn, WaR, Vege) were omitted, to maintain the homogeneity of the datasets in question. All values reported below the Limit of Detection (LoD) or the Limit of Quantification (LoQ) were replaced by these respective limit values, and these values were flagged. For the survey-based datasets (SCARCE, JDS3), the average of all values of a single

Table 1
Overview of sources for observed concentration data.

Dataset	References	No. of chemicals[a]	No. of stations	Frequency and period
Joint Danube Survey 3 (JDS3)	Liška et al. (2015)	204	51 stations along the Danube River	single survey, 13 August to 26 September 2013
RIWA-Rijn database (RIWA-Rijn, Nieuwegein)	https://www.riwa-rijn.org/en/	111	Lobith (border of Germany and The Netherlands)	2010–2015, appr. monthly frequency
Office for Environment and Energy Basel-Stadt screening data (WaR)	Mazacek et al. (2016)	100	Weil am Rhein (border of Switzerland and Germany)	2012–2016, often daily frequency
SCARCE database	Navarro-Ortega et al. (2012)	103	24 in Ebro basin, 24 in Guadalquivir basin, 15 in Júcar basin, 14 in Llobregat basin	2–4 samples during surveys in September-October 2010 and June-November 2011
Swedish Pesticides monitoring (Vege)	Gustavsson et al. (2015)	34	1 station in Vege River	2002–2013, 54–107 analyses per substance

[a] Number of chemicals satisfying requirements as discussed in the text (> 10% un-flagged values).

chemical per station and next the average of the values of all stations per chemical were calculated. The percentage of un-flagged values (not affected by LoD/LoQ) per station and for the average over all stations were also calculated. For the datasets with temporal coverage (RIWA-Rijn, WaR, Vege), the average of all values of a single chemical was calculated, as well as the percentage of un-flagged values. We found that 10% of un-flagged values were sufficient to approach the observed average value within a factor of 2 (S4). Note that we used averages here instead of medians, because averages are better preserved than medians if the number of unaffected analysis results decreases.

CMFA accuracy was evaluated for all substance/basin combinations where emission data and field data were available. Results were extracted at the exact location of the corresponding sampling sites (Fig. 1). For the survey-based datasets, output was used from the survey periods (13 August to 26 September 2013 for JDS3, September-October in 2010 and 2011 for SCARCE). For the single station datasets output was used for longer periods (2011–2013 for RIWA-Rijn and WaR, 2010–2013 for Vege).

The implications of the CMFA (in-)accuracy were demonstrated by conducting a substance prioritization exercise for the Danube River Basin following the NORMAN prioritization framework (Dulio and von der Ohe, 2013; S7). The objective of such an exercise was to determine substances relevant for undesirable effects in surface waters. While commonly based on measured concentrations, the prioritization was now driven by CMFA derived concentrations. By repeating the exercise with different perturbations of the CMFA concentrations (consistent with the expected inaccuracy), the sensitivity of the prioritization results to the CMFA accuracy was established.

3. Results

3.1. CMFA application to Europe: estimated emissions

Data to estimate emission were available for 621 pharmaceuticals, 408 pesticides and 4159 REACH registered organic chemicals. 39 pesticides and 46 REACH registered chemicals were also registered as biocides. For substances present in more than one category, pharmaceutical data take preference, next pesticide data and finally REACH data. For all chemicals, spatially and temporally variable emissions were estimated Europe-wide for $2009-2013$. The annually averaged results are illustrated for a few example chemicals in Table 2.

For the pesticide Terbuthylazine (CAS 5915-41-3) the losses to surface water and soil are passed directly as emissions to the surface water and the soil compartments. The data show that losses to surface waters constitute 1% of the total. This is a feature of the input dataset we used. The cumulative results for the pharmaceutical Sulfamethoxazole (CAS 723-46-6) show a more complex picture. All losses are to wastewater ((2) in Table 2), which is for the largest part routed to WWTPs (7) and for a minor part via unsewered areas (6) to soils and surface water (10)(11). The part routed to WWTPs is partly removed (14), partly reaches the surface water via effluents (13), while a small share is redistributed to soils via re-use of sludge (12). For the REACH chemical Benzotriazole (CAS 95-14-7), part of the losses is to wastewater as for pharmaceuticals and part of the losses is to soils as for pesticides. Fig. 3 shows examples of the spatial distribution of the estimated emissions to surface waters (16). For the pesticide Terbuthylazine (CAS 5915-41-3), the variable use intensity between countries in our input data is clearly visible. Within countries, spatial gradients are controlled by land-use. For the REACH chemical Benzotriazole (CAS 95-14-7), the use intensity is defined at the European level. Spatial differences are controlled by population density, standard of living and waste water management.

3.2. CMFA application to Europe: fate and transport

Fate and transport calculations were analysed for the chemical/

basin combinations relevant for the validation. Table 3 and Fig. 4 show mass balances for example chemicals for the Danube basin.

The pesticide Terbuthylazine (CAS 5915-41-3) shows significant removal in soils (2) and some removal in surface waters (8), while most of the mass that reaches the surface water (6)(7) is exported (10). The pharmaceutical Sulfamethoxazole (CAS 723-46-6) and the REACH chemical Benzotriazole (CAS 95-14-7) both show very low removal (2) (8), while almost all mass that reaches the surface waters (6)(7) is exported (10). Some mass is accumulating in soils (5). The balance check was not always exactly equal to zero, due to small inaccuracies in the Delft3D-WAQ engine of the fate and transport model.

Fig. 5 and Fig. 6 illustrate the spatial and temporal variation across Europe of the simulated concentrations of the pesticide Terbuthylazine and the REACH chemical Benzotriazole. The median (P_{50}) concentrations during 2013 show the spatial variability, while the temporal variability is illustrated by the difference between the P_{99} and the P_{50}, plotted using the same scale.

The Europe-wide CMFA was run for a subset of 1785 chemicals, for which sufficient toxicity data could be collected and the results were successfully used to produce a mixture risk assessment for aquatic species assemblages (Posthuma et al., 2019), while it was demonstrated that an increased mixture risk results in a lower ecological status class (Posthuma et al., in press).

3.3. CMFA accuracy

The simulated surface water concentrations could be compared to measured concentrations for 226 substance/basin combinations (146 substances in 1–5 basins). CMFA accuracy was expressed by the absolute logarithmic error $E = {}^{10}\log(\overline{C}_m) - {}^{10}\log(\overline{C}_f)$, where $\overline{C}_m$ denotes the average simulated concentration and $\overline{C}_f$ the average measured concentration. This error metric was considered appropriate in view of the sometimes large differences encountered between measured and simulated concentrations for individual substances. Note that the use of average concentrations has already been discussed in the Materials and

Table 2
Aggregated emission estimates (tons/year) over the total EU28Plus domain for selected substances.

CAS Name Group	a	5915-41-3 Terbuthylazine Pest	723-46-6 Sulfamethoxazole Pharma	95-14-7 Benzotriazole Reach
Losses to soil	(1)	1487	0	49.0
Losses to wastewater	(2)	0	25.94	193.5
Losses to surface water	(3)	20	0	0.0
Total losses		1507	25.94	242.5
Soil to unpaved	(4)	1487	0	46.6
Soil to paved	(5)	0	0	2.4
Wastewater unsewered	(6)	0	2.77	20.4
Wastewater to WWTPs	(7)	0	23.17	173.1
Unpaved to SGW	(8)	1487	0	46.6
Paved to SW	(9)	0	0	0.6
Paved to WWTP	(9a)	0	0	1.8
Unsewered to SGW	(10)	0	2.71	20.0
Unsewered to SW	(11)	0	0.06	0.4
WWTP sludge reused	(12)	0	0.07	0.7
WWTP effluents	(13)	0	11.35	166.0
Removal at WWTPs	(14)	0	11.75	6.4
Total to SGW	(15)	1487	2.78	67.4
% of total losses		99%	11%	28%
Total to SW	(16)	20	11.41	167.0
% of total losses		1%	44%	69%

WWTP = wastewater treatment plant; SGW = soil and groundwaterl SW = surface water.

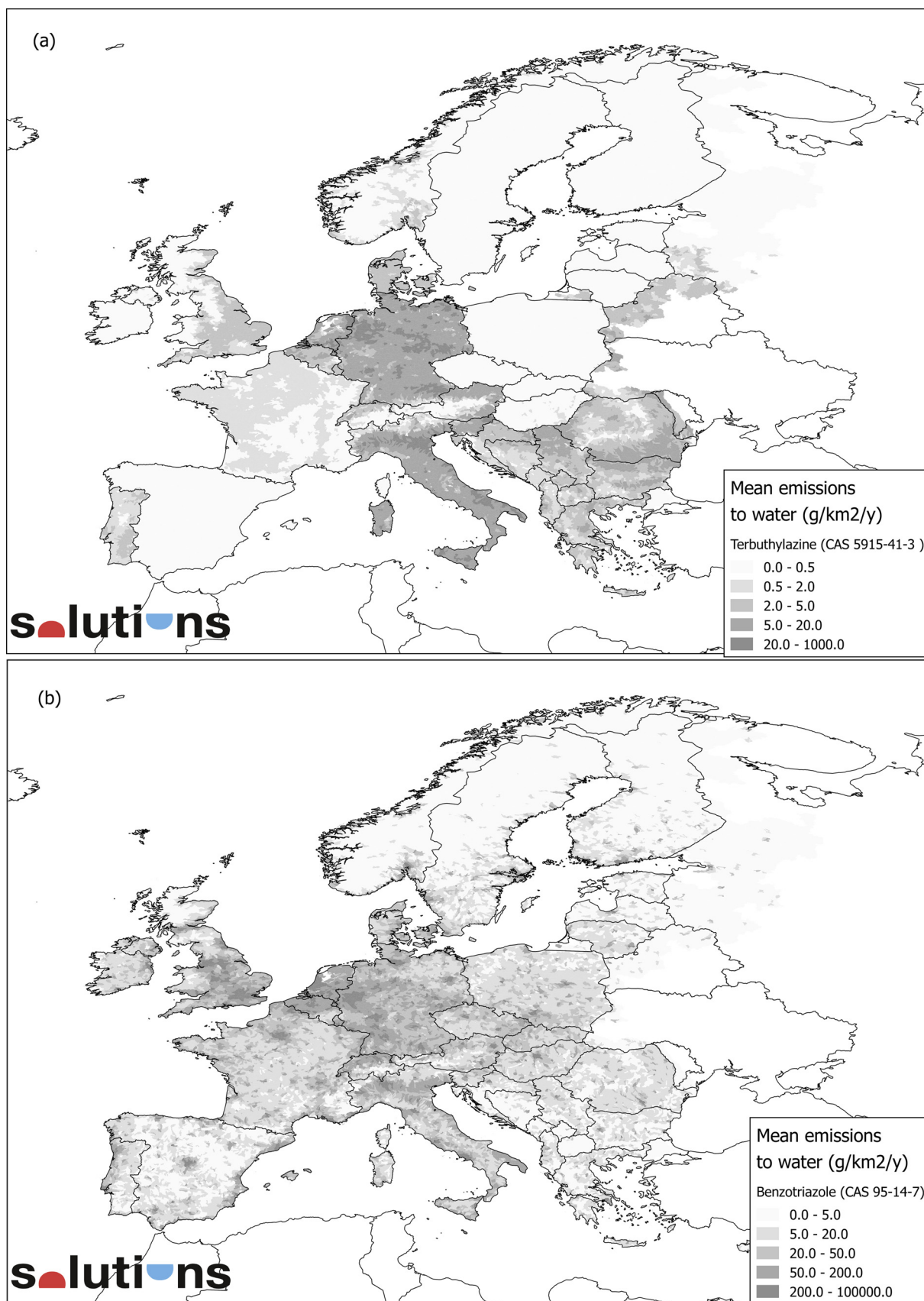a Numbers for all tabulated terms refer to Fig. 2 where their meaning is shown.

Fig. 3. Estimated annually averaged direct emissions to water (g/km2/y) of Terbuthylazine (a) and Benzotriazole (b).

Table 3
Calculated mass balances for the Danube River Basin for selected chemicals.

CAS		5915-41-3	723-46-6	95-14-7
Name		Terbuthylazine	Sulfamethoxazole	Benzotriazole
Group	[a]	Pest	Pharma	Reach
Soil and groundwater (SGW) balances (tons/year)				
Emissions to SGW	(1)	228.6	0.487	8.86
Removal in SGW	(2)	−189.6	−0.002	−0.01
To deep GW	(3)	0.0	0.000	0.00
To SW	(4)	42.5	0.270	5.91
Storage in SGW	(5)	3.5	−0.215	−2.94
Surface water (SW) balances (tons/year)				
Emissions to SW	(6)	3.1	1.186	17.00
From SGW	(7)	42.5	0.270	5.91
Removal in SW	(8)	−5.4	−0.004	0.00
Storage Sediments	(9)	−0.2	0.000	0.00
Export	(10)	−40.9	−1.442	−22.72
Storage in SW	(11)	1.1	−0.011	−0.19
Balance check		0.2	−0.001	0.00
Surface water balances (%)				
Emissions to SW	(6)	7%	81%	74%
From SGW	(7)	93%	19%	26%
Removal in SW	(8)	−12%	0%	0%
Storage Sediments	(9)	0%	0%	0%
Export	(10)	−90%	−99%	−99%
Storage in SW	(11)	2%	−1%	−1%
Balance check		0%	0%	0%

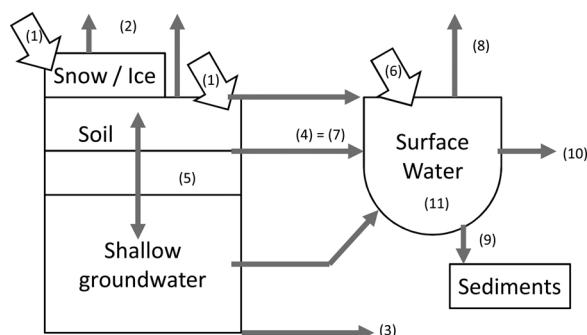[a] Numbers for all tabulated terms refer to Fig. 4 where their meaning is shown.

Fig. 4. Schematic overview of compartments and pathways included in the fate and transport model. Numbers refer to Table 3.

Methods section. Fig. 7 shows the histogram of the error. Table 4 provides the statistics of the error across datasets and across substances groups.

The average error is effectively zero (-0.01) and the standard deviation is 1.20. In 65% of cases the error is between 1 and +1 (below one order of magnitude), while in 90% of cases the error is between -2 and +2 (below two orders of magnitude). Within the validation data set, pharmaceuticals account for 46% of cases, pesticides for 35% and the largest group of REACH registered chemicals for only 18%. Concentrations of pharmaceuticals were generally underpredicted, while those of pesticides and REACH registered chemicals were generally overpredicted. The standard deviation of the error is smallest for pesticides and highest for REACH registered chemicals. Looking at individual data sets, the mean error does not vary a lot. Neither does the standard deviation of the error, with slightly lower values for the datasets with time series (RIWA-Rijn, WaR, Vege). The complete validation table is provided in S5. These results were obtained after the exclusion of highly volatile substances (boiling point < 431 K), for which the accuracy was very poor.

3.4. Implications of CMFA accuracy: substances prioritization

The substances prioritization exercise was conducted for 332 chemicals, using CMFA concentrations (S7). The CMFA concentrations were perturbed by a factor 0.01, 0.1, 1.0, 10 and 100 respectively, reflecting uncertainty stemming from concentration errors of up to 2 orders of magnitude as in 90% of validation cases. This provided not one but 5 risk scores per substance, reflecting the uncertainty stemming from CMFA accuracy. Risk scores exceeding a significance threshold of 0.05 were found for 20 chemicals, regardless of CMFA accuracy ("true positives"). Risk scores below the significance threshold were found for 63 chemicals, regardless of CMFA accuracy ("true negatives"). For these 83 chemicals, CMFA inaccuracy is not affecting the prioritization result. The remaining 249 chemicals were found to potentially exceed the threshold. The outcome is indecisive, as a result of CMFA accuracy.

4. Discussion

4.1. Factors driving CMFA accuracy

CMFA as presented here aims to provide information to complement monitoring data in support to water management. The accuracy of the simulated concentrations is the aggregated result of the accuracy of the hydrology, emissions, fate and transport and substance properties models, in combination with the necessity to refrain from using detailed substance-specific input data and carry out substance-by-substance model calibration. The underlying hydrology model was already available and validated (Hundecha et al., 2016) and is not further discussed here.

4.1.1. Pharmaceuticals

For pharmaceuticals, we assumed a single use type and one dominant, well-defined pathway to surface waters via WWTPs (next to a pathway via redistributed sewage sludge (Table 2), while use as veterinary pharmaceuticals could not be addressed). Therefore, we expected to obtain relatively accurate results. Oldenkamp et al. (2018) reported an accuracy within one order for 95% of 35 cases for the Rhine and Ouse basins (61% in our results; N = 105). One possible cause for the lower accuracy in our results is the extrapolation of consumption data from UK and Sweden to the rest of Europe. Comparison of the per capita sales data in the UK and Sweden for individual substances shows that differences exist up to several orders of magnitude. This suggests that the extrapolation of consumption data to other countries can indeed be expected to provide inaccuracies of several orders of magnitude. Oldenkamp et al. (2018) used consumption data from UK, The Netherlands, Germany, France and Switzerland for the 35 modelled substances, and therefore only marginally relied on extrapolation. Excretion rates and the fate in treatment plants were investigated and discarded as significant causes of inaccuracy (S8). Thus, the availability and accuracy of consumption data was found to be the key factor determining CMFA accuracy.

4.1.2. Pesticides

For pesticides, we also assumed a single use type (application in agriculture), which was expected to lead to relatively accurate results. Just as for pharmaceuticals however, use volumes differ strongly between countries, but were not available everywhere. This affects the Danube results, as pesticide emission data were only available for Germany, Austria, Hungary, Czech Republic, Slovakia and Slovenia, and not for the other states in the Danube catchment, including large countries like Romania, Bulgaria and Serbia. Danube Basin simulations appeared to be driven by extrapolated emission data for large parts of the basin. The same holds for the Rhine at Weil am Rhein, because most of the upstream catchment is on Swiss territory, where there were no emission data. For surveys (SCARCE and JDS3), the fit between model and data was anyhow expected to be imperfect, due to variations in
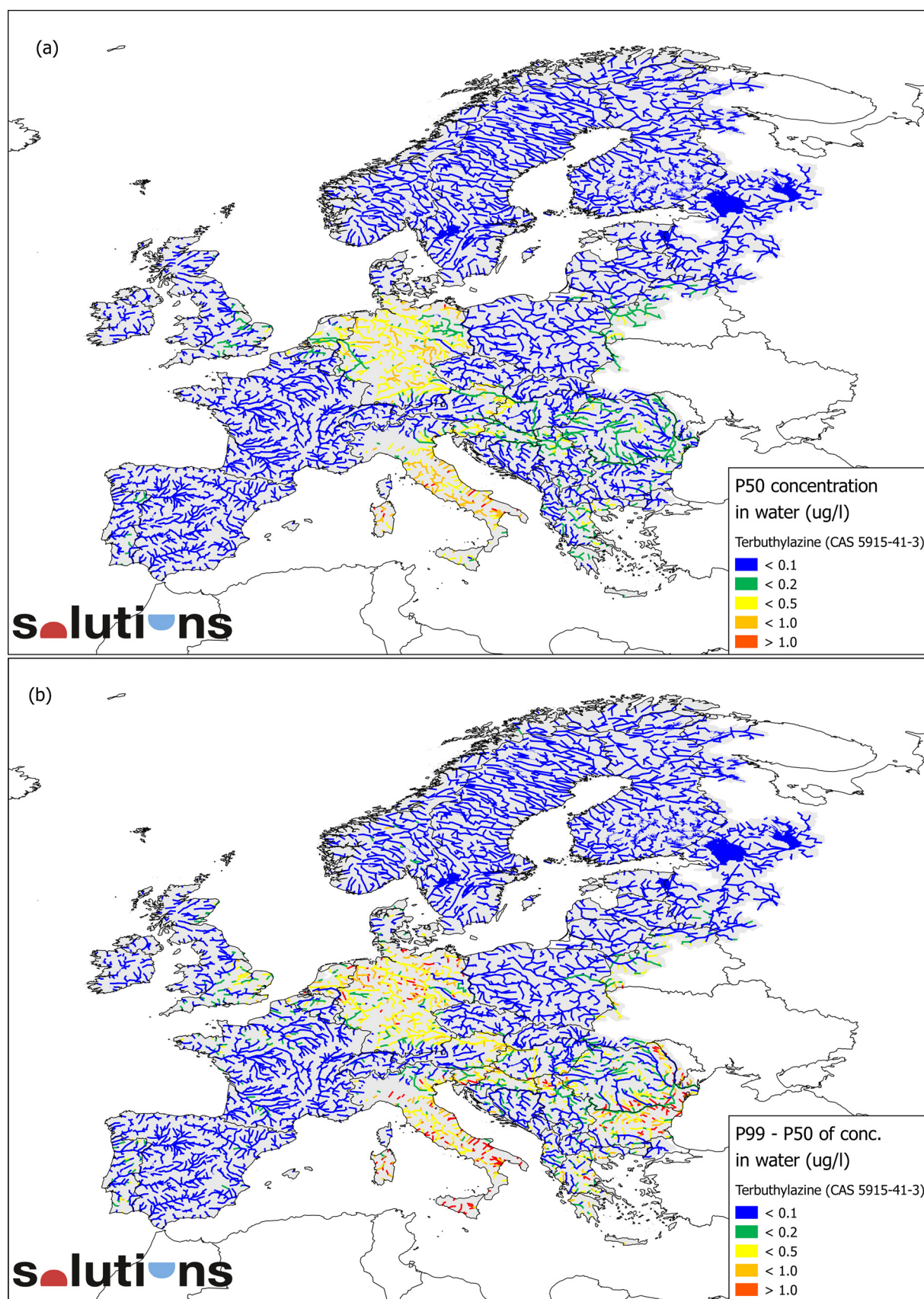
Fig. 5. Median of simulated total concentrations (μg/l) of Terbuthylazine (a), and the difference between the P₉₉ and the median (b). Simulations were based on the hydrological year 2013.
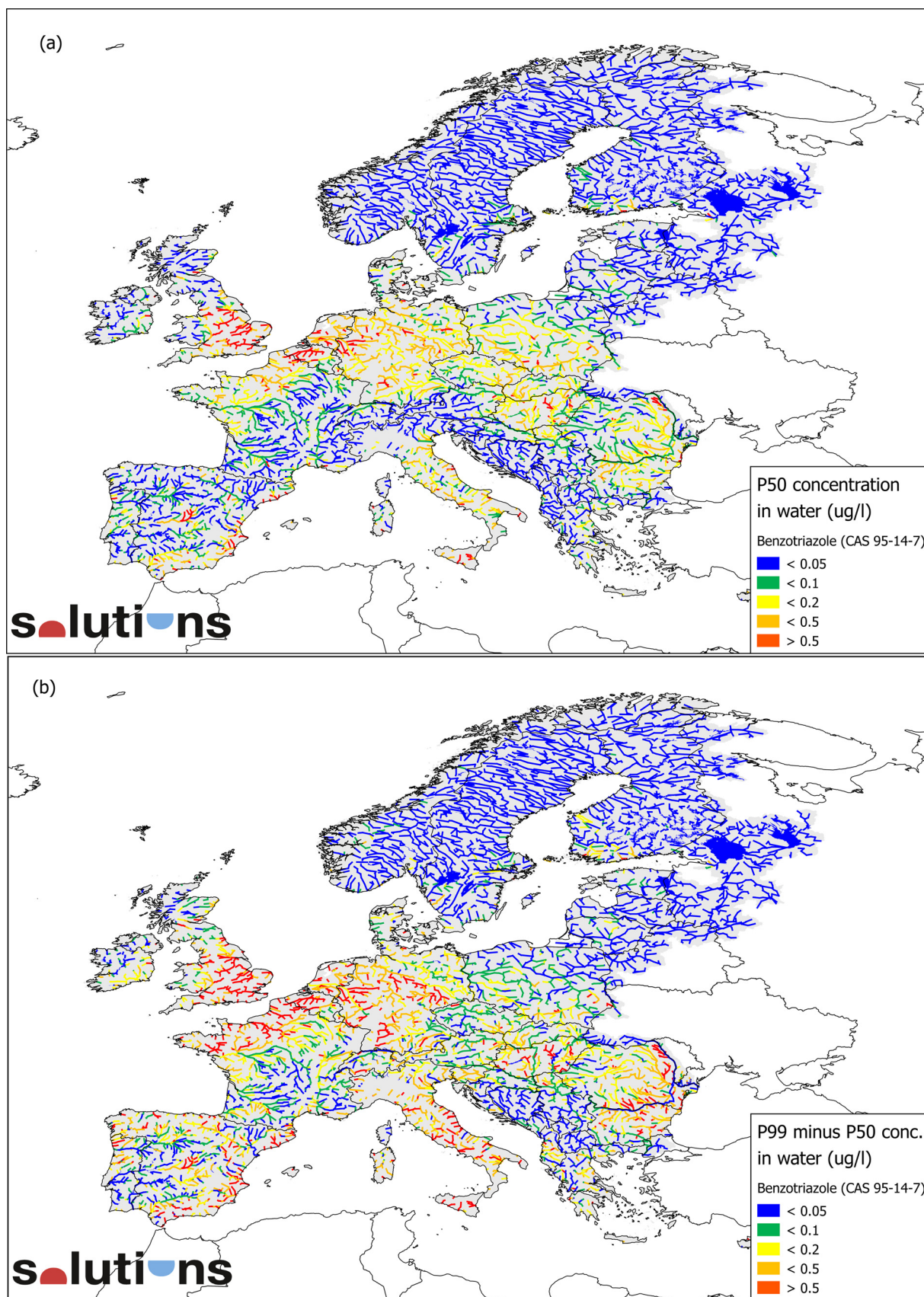
Fig. 6. Median of simulated total concentrations (μg/l) of Benzotriazole (a), and the difference between the P₉₉ and the median (b). Simulations were based on the hydrological year 2013.
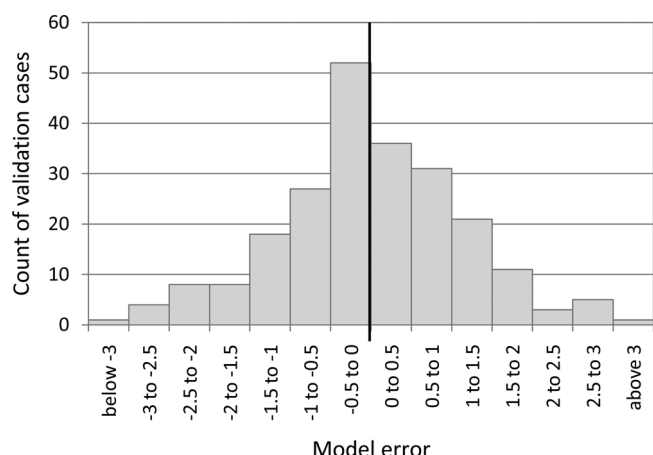
Fig. 7. Histogram of error in 226 substance/basin combinations used for CMFA evaluation (classes refer error defined as absolute logarithmic error of the simulated versus measured concentrations; fat line refers to perfect agreement).

surface water concentrations not captured by surveys. For these reasons, the best fit between model and data was expected and achieved for the Rhine at Lobith and for the Vege River. The assumption that application in agriculture is the dominant use type for pesticides has not been investigated in-depth. It may have to be adjusted for substances used as biocides in the urban environment (anti-fouling on buildings, private and public green areas). Munz et al. (2017) observed that the detection frequency of pesticides in Swiss rivers correlates with the fraction of arable land in the catchment. This supports our assumption that the use in agriculture is the dominant pathway. In contrast, Ginebreda et al. (2017) did not find such a correlation in Spain.

4.1.3. REACH registered chemicals

The large group of REACH registered chemicals has diverse and often multiple use types. To estimate their emissions, we relied on information from the REACH registration dossiers. Information about the chemicals use volumes is only available to Member State Competent Authorities for specific regulatory purposes. The public extracts of the registration dossiers (https://echa.europa.eu/) contain only so-called tonnage bands (specifying just a lower limit ("10,000 + ") or a range ("10,000–100,000") and not for all substances. For this study, we had access to the confidential use volumes. We found that the public tonnage band information was accurate if it was available. We also found that the model error was not significantly affected by the difference between the actual tonnage and the logarithmic middle of the band (i.e. 31,600 for the 10,000–100,000 band, etc.). Using public tonnage band data, if available, was just as accurate as using confidential use volumes. The average error for the 40 REACH registered chemicals validation cases amounts to 0.3, with a standard deviation of 1.27 (Table 4). On average, the concentration was overestimated by a factor 2 ($10^{0.3}$). The strong scatter of the error among the 40 REACH substances is probably caused by the lack of substance specific loss rates.

Several use characteristics of a chemical are reported in the REACH dossiers, and information about potential losses to the environment is provided in the form of so-called Environmental Release Categories (ERCs; ECHA, 2015). The REACH Guidance (ECHA, 2016) provides default worst-case release factors resulting from the conditions of use described in the ERCs. Specific Environmental Release Categories (spERCs; CEFIC, 2012) detail the ERCs and provide best estimates of environmental release for 169 possible uses. These spERCs have been the basis for estimating generic loss factors for REACH substances in this study. The information in the REACH dossiers is insufficient to predict substance releases (e.g. Schulze et al., 2018). A key limitation is that most dossiers mention multiple uses for a single chemical, but the share of the use volume connected to each use is not specified. As the ERCs and the spERCs show strongly varying loss fractions between uses, the actual loss fraction cannot be quantified. Systems to classify chemicals with respect to the likelihood to be emitted to the environment based on semi-quantitative indicators have been reported in the literature, mostly for ranking purposes (Schulze et al., 2018). Oltmanns et al. (2018) used the ERC references in the REACH registration dossiers and the REACH Guidance default worst-case release factors to estimate likelihood of emission. They used the ERC with the highest worst-case release factor to classify the substance. We investigated if this method would allow differentiation of loss rates between substances and reducing the scatter of the model error among substances. This effort was not successful, because the method offered a poor discrimination between substances, with 28 out of 40 substances ending up in the 100% worst case release category, often as a result of multiple substance uses with highly variable ERCs (S6). Apart from use volumes and loss factors, the fate in WWTPs and the retention in the surface waters may (partly) explain the error. For the 40 substances, the simulated fraction passing WWTPs into the effluent varied in a wide range between 2% and 98% (average 34%, SD 38%, N = 40). The simulated retention in the surface waters varied between 1% and 69% (average 15%, SD 14%, N = 40). We found no correlation between the model error and these two indicators. Based on the above, we consider the use of substance independent release fractions to be the likely cause for model inaccuracies.

4.1.4. Fate and transport

The fate and transport model STREAM-EU has already been validated for specific substances, using dedicated emission estimates (pharmaceuticals in Nordic countries: Lindim et al., 2017; PFAS in EU river basins: Lindim et al., 2016b). This suggests that the major limiting factor for the accuracy of the fate and transport model is the accuracy of the input data that need to be provided for a large spectrum of chemicals and not the capabilities of the model itself. A modelling study using STREAM-EU for 16 pharmaceuticals in The Netherlands showed very good agreement between measured and simulated concentrations at up to 37 stations across the country (unpublished data). Apart from the emissions discussed above, the characterization of substance degradability is important, which we did by using the CATALOGIC biodegradation model that predicts biodegradation under OECD 301C test

Table 4

Statistics of error defined as the absolute logarithmic error of the simulated versus measured concentrations, across basins/data sets and across chemicals groups. N refers to the number of substance/basin combinations.

	Pesticides			Pharmaceuticals			REACH registered			All substances		
	N	Av	StD	N	Av	StD	N	Av	StD	N	Av	StD
JDS3	21	0.74	1.06	27	−1.24	1.15	15	0.68	1.11	63	−0.12	1.46
RIWA-Rijn	13	0.30	0.93	17	−0.66	0.72	9	0.22	1.22	39	−0.13	1.01
SCARCE	17	0.18	1.09	41	0.27	1.11	11	0.15	1.47	69	0.23	1.15
Vege	20	0.17	0.91							20	0.17	0.91
WAR	10	0.68	0.85	20	−0.64	0.78	5	−0.32	1.37	35	−0.22	1.05
All Data	81	0.40	0.99	105	−0.44	1.17	40	0.30	1.27	226	−0.01	1.20

Av = average; StD = standard deviation.

conditions (Dimitrov et al., 2011; S3).

4.1.5. Limitations

In the current approach we neglected production losses. We also note that the spatial distribution method used, based on population and standard of living is most suited for chemicals with wide dispersive use. Specific chemicals with a dominant use type may be better modelled using more specific spatial distribution algorithms. The current approach is focusing on emerging chemicals, with current emissions explaining exposure. We did not attempt to include legacy substances, for which "secondary emissions" are important where chemicals are re-released from contaminated sediments and soils.

4.2. Improving CMFA accuracy

Assuming that the results of the CMFA validation are representative also for chemicals not included in the validation datasets, simulated concentrations for a wide range of chemicals on a continental scale can only be generated with errors spanning up to 2 orders over- or under-estimation. The substances prioritization example presented above shows that this affects the usability of the information generated: indecisive results were obtained for 249 out of 332 chemicals. It could be argued that using monitoring results for substances prioritization also leads to significant uncertainty, as well as the quantification of hazard. Increasing the CMFA accuracy however would definitely increase credibility, acceptance and usability. For illustration, reducing the CMFA error from two to one order of magnitude in the substances prioritization exercise would increase the number of true positives from 20 to 64 and the number of true negatives from 63 to 126, and would reduce the count of undecisive results from 249 to 142.

The key to reducing uncertainty in exposure modelling is improving the quality of chemical input data (ECETOC, 2018). For substances with a well-defined single use type (pesticides, pharmaceuticals), this can be achieved by acquiring accurate regionalized use volume information. Such information is unfortunately rarely available in the public domain, which limits the capabilities of water management authorities to fulfil their obligations set in the WFD. For substances with multiple use types (such as many substances currently regulated under REACH), this paper argues that methods to quantify the fractions lost to the environment out of the total volume used are lacking. Pending a more rigorous registration of chemicals use types, a practical way forward could be to study observed concentrations in wastewater, stormwater, rural runoff etc. throughout Europe of a wider group of substances and try to link this to information about substance properties and substance use obtained from mining of public data sources.

More work is also needed to alleviate current limitations in predicting biodegradation across large groups of organic chemicals, and across the water, soil and sediment compartments (Junker et al., 2019). Also, the sorption sub-model used here (SI) assumes that only the non-dissociated neutral form of the organic acid or base sorbs to organic matter. This works reasonably well for anions but not for cations (ECETOC, 2013). Sorption models for organic cations are under development (Droge and Goss, 2013), but are far from being applicable to a wide range of cationic substances.

In addition, we found that alternative substance dependent input data obtained from different sources typically show large differences. Only by sharing data and methods this could be avoided and scientific innovation for the benefit of water quality protection and management be enhanced.

5. Conclusions

This paper demonstrates that it is possible to provide a consistent European scale time and space resolved image of emissions and concentrations by computational material flow analysis supported by mathematical modelling for thousands of organic chemicals. This kind of modelling can complement results obtained from monitoring by covering substances, sites and times not included in field data sets, and those of models used in generic chemical safety assessments. The chosen method allows application to many chemicals together, which is a prerequisite for and a first step towards predicting "real-life" mixture effects and eventually judging the concept of a "non-toxic environment" (http://ec.europa.eu/environment/chemicals/non-toxic/index_en.htm). Furthermore, the chosen method resolves the cause-effect chain from the use of chemicals to their effects in European water systems, which allows a prognosis of the effects of abatement measures and the changes expected from socio-economic trends. The comparison of simulated concentrations for 226 substance/basin combinations showed that the simulated concentrations were correct on average. For 65% of substance basin combinations the error was within one order of magnitude, while for 90% of cases the error was within two orders of magnitude. It was demonstrated how the current results can be used for a substances prioritization, taking into account the relatively large uncertainty. The inaccuracy of the available use volume or use type information is expected to be the main cause of uncertainty. Suggestions to improve the CMFA accuracy are provided, implementation of which would definitely increase credibility, acceptance and usability.

Authors contributions

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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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.2020.122655.

References

Boxall, A., et al., 2012. Pharmaceuticals and personal care products in the environment: what are the big questions? Environ. Health Perspect. 120, 1221–1229. https://doi.

org/10.1289/ehp.1104477.

Brack, W., et al., 2017. Towards the review of the European Union Water Framework Directive: recommendations for more efficient assessment and management of chemical contamination in European surface water resources. Sci. Total Environ. 576, 720–737. https://doi.org/10.1016/j.scitotenv.2016.10.104.

CEFIC, 2012. Specific Environmental Release Categories (SPERCs) — Chemical Safety Assessments, Supply Chain Communication and Downstream User Compliance. Report by the Cefic SPERC Core Team, revision 2. Brussels, October 2012. .

Dimitrov, S., Pavlov, N., Dimitrova, D., Georgieva, D., Nedelcheva, A., Kesova, R., Vasilev, O., Mekenyan, O., 2011. Simulation of chemical metabolism for fate and hazard assessment. II CATALOGIC simulation of abiotic and microbial degradation. SAR and QSAR. Environ. Res. 22, 719–755. https://doi.org/10.1080/1062936X.2011.623322.

Droge, S., Goss, K.-U., 2013. Development and evaluation of a new sorption model for organic cations in soil: contributions from organic matter and clay minerals. Environ. Sci. Technol. 47, 14233–14241. https://doi.org/10.1021/es4031886.

Dulio, V., von der Ohe, P. (Eds.), 2013. NORMAN Prioritisation Framework for Emerging Substances. NORMAN Association. 70 pp., ISBN: 978-2-9545254-0-2. Available: https://www.normandata.eu/sites/default/files/norman_prioritisation_manual_15% 20April2013_final_for_website.pdf. (Accessed 9 July 2019).

ECETOC, 2013. Environmental Exposure Assessment of Ionisable Organic Compounds. Technical Report No. 123. Brussels, December 2013, Available: http://www.ecetoc.org/wp-content/uploads/2014/08/ECETOC-TR-123-Environmental-risk-assessment-of-ionisable-compounds.pdf. (Accessed 13 July 2019). .

ECETOC, 2018. Advances in (Environmental) Exposure Modelling: Bridging the Gap Between Research and Application. Workshop Report No. 35. Brussels, March 2018, ISSN-2078-7219-35. Available: http://www.ecetoc.org/wp-content/uploads/2018/03/ECETOC-WR-35.-Advances-in-environmental-exposure-modelling.pdf. (Accessed 7 July 2019). .

ECHA, 2015. Chapter R.12: Use description. Guidance on Information Requirements and Chemical Safety Assessment. . Available: https://echa.europa.eu/documents/10162/13632/information_requirements_r12_en.pdf/ea8fa5a6-6ba1-47f4-9e47-c7216e180197. (Accessed 6 December 2018).

ECHA, 2016. Chapter R.16: Environmental exposure assessment. Guidance on Information Requirements and Chemical Safety Assessment. . Available: https://echa.europa.eu/documents/10162/13632/information_requirements_r16_en.pdf. (Accessed 6 December 2018).

EEA, 2018. European Waters: Assessment of Status and Pressures 2018. https://doi.org/10.2800/303664.

European Commission, 2012. Guidance Document No. 28 Preparation of an Inventory of Emissions, Discharges and Losses of Priority and Priority Hazardous Substances. https://doi.org/10.2779/2764.

Ferrer, D., DeLeo, P., 2017. Development of an in-stream environmental exposure model for assessing down-the-drain chemicals in Southern Ontario. Water Qual. Res. J. Canada 52 (4), 258–269. https://doi.org/10.2166/wqrj.2017.019.

Funk, M., Ash, C., 2020. A cleaner, greener future for chemicals. Science 367 (6476), 378–379. https://doi.org/10.1126/science.aba8242.

Ginebreda, A., López de Alda, M., Barceló, D., van Gils, J., Slobodnik, J., 2017. Guidance for Identification of RBSPs in Mediterranean River Basins and List of RBSP Including Quantification of Their Ecological Impact and Modeling–based Exposure and Risk Predictions Validated. Available: https://www.solutions-project.eu/wp-content/uploads/2018/11/D21-1_Iberian_CSICNORMAN-priorit-AKor-review_JS-2_FINAL.pdf. (Accessed 7 July 2019). .

Gustavsson, M., Kreuger, J., Bundschuh, M., Backhaus, T., 2015. Pesticide mixtures in the Swedish streams: environmental risks, contributions of individual compounds and consequences of single-substance oriented risk mitigation. Sci. Total Environ. 598, 973–983. https://doi.org/10.1016/j.scitotenv.2017.04.122.

Huber, W.C., 1986. Deterministic modeling of urban runoff quality. In: Torno, H.C., Marsalek, J., Desbordes, M. (Eds.), Urban Runoff Pollution. NATO ASI Series Vol. 10. Springer, Berlin, Heidelberg, Germany, pp. 167–242.

Hundecha, Y., Arheimer, B., Donnelly, C., Pechlivanidis, I., 2016. A regional parameter estimation scheme for a pan-European multi-basin model. J. Hydrol. Reg. Stud. 6, 90–111. https://doi.org/10.1016/j.ejrh.2016.04.002.

IKSR, 2009. Evaluation Report Human Pharmaceuticals. Technical Report 182 (in German). International Commission for the Protection of the Rhine River. Appendix, 10pp. Available: https://www.iksr.org/fileadmin/user_upload/DKDM/Dokumente/Fachberichte/DE/rp_De_0182a_Anlage.pdf. (Accessed 7 July 2019).

Junker, T., Coors, A., Schüürmann, G., 2019. Compartment-specific screening tools for persistencs: potential role and application in the regulatory context. Integr. Environ. Assess. Manag. 15, 470–481.

Kapo, K., DeLeo, P., Vamshi, R., Holmes, C., Ferrer, D., Dyer, S., Wang, X., White-Hull, C., 2016. iSTREEM®: an approach for broad-scale in-stream exposure assessment of "down-the-drain" chemicals. Integr. Environ. Assess. Manag. 12, 782–792. https://doi.org/10.1002/ieam.1793.

Kehrein, N., Berlekamp, J., Klasmeier, J., 2015. Modeling the fate of down-the-drain chemicals in whole watersheds: new version of the GREAT-ER software. Environ. Model. Softw. 64, 1–8. https://doi.org/10.1016/j.envsoft.2014.10.018.

Kortenkamp, A., Ermler, S., Scholze, M., Faust, M., Backhaus, T., Posthuma, L., de Zwart, D., Focks, A., Baveco, H., van Gils, J., 2018. Common Assessment Framework for HRA and ERA Higher Tier Assessments Including Fish and Drinking Water and Multi-species ERA Via SSD, Population-level ERA Via IBM and Food Web Vulnerability ERA. Available: https://www.solutions-project.eu/wp-content/uploads/2018/11/D18.1_SOLUTIONS-D18_1-after-peer-review-clean-V2_Kortenkamp_chm_with_annex.pdf. (Accessed 7 July 2019). .

Kroeze, C., Gabbert, S., Hofstra, N., Koelmans, A., Li, A., Löhr, A., Ludwig, F., Strokal, M., Verburg, C., Vermeulen, L., van Vliet, M., de Vries, W., Wang, M., van Wijnen, J., 2016. Global modelling of surface water quality: a multi-pollutant approach. Curr. Opin. Environ. Sustain. 23, 35–45. https://doi.org/10.1016/j.cosust.2016.11.014.

Lindim, C., van Gils, J., Cousins, I., 2016a. A large-scale model for simulating the fate & transport of organic contaminants in river basins. Chemosphere 144, 803–810.

https://doi.org/10.1016/j.chemosphere.2015.09.051.

Lindim, C., van Gils, J., Cousins, I., 2016b. Europe-wide estuarine export and surface water concentrations of PFOS and PFOA. Water Res. 103, 124–132. https://doi.org/10.1016/j.watres.2016.07.024.

Lindim, C., van Gils, J., Georgieva, D., Mekenyan, O., Cousins, I., 2016c. Evaluation of human pharmaceutical emissions and concentrations in Swedish river basins. Sci. Total Environ. 572, 508–519. https://doi.org/10.1016/j.scitotenv.2016.08.074.

Lindim, C., Cousins, I., vanGils, J., Kühne, R., Kutsarova, S., Mekenyan, O., 2017. Model-predicted occurrence of multiple pharmaceuticals in Swedish surface waters and their flushing to the Baltic Sea. Environ. Pollut. 223, 595–604. https://doi.org/10.1016/j.envpol.2017.01.062.

Liška, I., Wagner, F., Sengl, M., Deutsch, K., Slobodník, J., 2015. Joint Danube Survey 3 A Comprehensive Analysis of Danube Water Quality. ICPDR – International Commission for the Protection of the Danube River, Vienna/Austria. ISBN: 978-3-200-03795-3. Available: http://www.danubesurvey.org/sites/danubesurvey.org/files/nodes/documents/jds3_final_scientific_report_1.pdf. (Accessed 7 July 2018).

Mazacek, J., Ruppe, S., Griesshaber, D., Langlois, I., Dolf, R., Singer, H., Leve, J., Hofacker, A., Leu, C., 2016. From accident to preventive monitoring. Aqua Gas 11, 66–75 (in German).

Munz, N., Burdon, F., de Zwart, D., Junghans, M., Melo, L., Reyes, M., Schönenberger, U., Singer, H., Spycher, B., Hollender, J., Stamm, C., 2017. Pesticides drive risk of micropollutants in wastewater-impacted streams during low flow conditions. Water Res. 110, 366–377. https://doi.org/10.1016/j.watres.2016.11.001.

Navarro-Ortega, A., Acuna, V., Batalla, R., Blasco, J., Conde, C., Elorza, F., Elosegi, A., Frances, F., La-Roca, F., Munoz, I., Petrovic, M., Pico, Y., Sabater, S., Sanchez-Vila, X., Schuhmacher, M., Barcelo, D., 2012. Assessing and forecasting the impacts of global change on Mediterranean rivers. The SCARCE Consolider project on Iberian basins. Environ. Sci. Pollut. Res. Int. 19 (4), 918–933. https://doi.org/10.1007/s11356-011-0566-5.

Nilsen, E., Smalling, K., Ahrens, L., Gros, M., Miglioranza, K., Picó, Y., Schoenfuss, H., 2019. Critical review: grand challenges in assessing the adverse effects of contaminants of emerging concern on aquatic food webs. Environ. Toxicol. Chem. 38, 46–60. https://doi.org/10.1002/etc.4290.

Nizzetto, L., Butterfield, D., Futter, M., Lin, Y., Allan, I., Larssen, T., 2016. Assessment of contaminant fate in catchments using a novel integrated hydrobiogeochemical-multimedia fate model. Sci. Total Environ. 544, 553–563. https://doi.org/10.1016/j.scitotenv.2015.11.087.

Oldenkamp, R., Hoeks, S., Čengić, M., Barbarossa, V., Burns, E., Boxall, A., Ragas, A., 2018. A high-resolution spatial model to predict exposure to pharmaceuticals in European surface waters: ePiE. Environ. Sci. Technol. 52, 12494–12503. https://doi.org/10.1021/acs.est.8b03862.

Oltmanns, J., Licht, O., Bitsch, A., Bohlen, M., Escher, E., Silano, V., MacLeod, M., Serafimova, R., Kass, G., Merten, C., 2018. Development of a novel scoring system for identifying emerging chemical risks in the food chain. Environ. Sci.: Processes Impacts 20, 340–353. https://doi.org/10.1039/C7EM00564D.

Pistocchi, A., Dorati, C., Aloe, A., Ginebreda, A., Marcé, R., 2019. River pollution by priority chemical substances under the Water Framework Directive: a provisional pan-European assessment. Sci. Total Environ. 662, 434–445. https://doi.org/10.1016/j.scitotenv.2018.12.354.

Posthuma, L., van Gils, J., Zijp, M., van de Meent, D., de Zwart, D., 2019. Species sensitivity distributions for use in environmental protection, assessment and management of Aquatic Ecosystems for 12386 Chemicals. Environ. Toxicol. Chem. 38 (4), 905–917. https://doi.org/10.1002/etc.4373.

Posthuma, L., Brack, W., van Gils, J., Focks, A., Müller, C., de Zwart, D., Birk, S., 2020. Mixtures of chemicals are important drivers of impacts on ecological status in European surface waters. Environ. Sci. Eur. 31, 71. https://doi.org/10.1186/s12302-019-0247-4.

Pullan, S., Whelan, M., Rettino, J., Filby, K., Eyre, S., Holman, I., 2016. Development and application of a catchment scale pesticide fate and transport model for use in drinking water risk assessment. Sci. Total Environ. 563–564, 434–447. https://doi.org/10.1016/j.scitotenv.2016.04.135.

Sala, S., Benini, L., Mancini, L., Pant, R., 2015. Integrated assessment of environmental impact of Europe in 2010: data sources and extrapolation strategies for calculating normalisation factors. Int. J. Life Cycle Assess. 20, 1568–1585. https://doi.org/10.1007/s11367-015-0958-8.

Schulze, S., Sättler, D., Neumann, M., Arp, H., Reemtsma, T., Berger, U., 2018. Using REACH registration data to rank the environmental emission potential of persistent and mobile organic chemicals. Sci. Total Environ. 625, 1122–1128. https://doi.org/10.1016/j.scitotenv.2017.12.305.

Schulze, S., Zahn, D., Montes, R., Rodil, R., Benito Quintana, J., Knepper, T., Reemtsma, T., Berger, U., 2019. Occurrence of emerging persistent and mobile organic contaminants in European water samples. Water Res. 153, 80–90. https://doi.org/10.1016/j.watres.2019.01.008.

Socialstyrelsen, 2015. http://www.socialstyrelsen.se/statistik/statistikdatabas/lakemedel. (Accessed 9 July 2019).

Stroomberg, G., Neefjes, R., de Jonge, J., Bannink, A., van de Haar, G., Zwamborn, C., 2018. Jaarrapport 2017, De Rijn. RIWA-Rijn, Nieuwegein, The Netherlands. ISBN 978-90-6683-168-1. Available: https://www.riwa-rijn.org/publicatie/jaarrapport-2017-de-rijn/. (Accessed 9 April 2019).

Struijs, J., 2014. SimpleTreat 4.0: A Model to Predict Fate and Emission of Chemicals in Wastewater Treatment Plants. Background Report Describing the Equations. RIVM Report 601353005/2014. Available: https://www.rivm.nl/bibliotheek/rapporten/601353005.pdf. (Accessed 9 July 2019).

UNESCO, HELCOM, 2017. Pharmaceuticals in the Aquatic Environment of the Baltic Sea Region — A Status Report. UNESCO Emerging Pollutants in Water Series – No. 1. UNESCO Publishing, Paris.

Wang, Z., Walker, G.W., Muir, D.C.G., Nagatani-Yoshida, K., 2020. Toward a global understanding of chemical pollution: a first comprehensive analysis of national and regional chemical inventories. Environ. Sci. Technol. 2020. https://doi.org/10.1021/acs.est.9b06379.