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Proposal for a tiered approach to evaluate the risk of transformation products formed from pesticide residues during drinking water treatment

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Abstract

Oxidative treatment methods are valuable tools for the microbial safety of drinking water. However, the reaction of oxidants with natural substances or anthropogenic contaminants present in the raw water can potentially lead to the formation of harmful transformation products (TPs). The present paper proposes a tiered approach for the risk evaluation of TPs formed from pesticide residues during drinking water treatment. First, the concentrations of pesticide residues in raw water used for drinking water production are evaluated (step 1). Substances with a predicted concentration in raw water above 0.1 µg/L proceed further to a reactivity assessment, examining the behavior in water treatment plants (step 2). Using information available in the scientific literature, prediction of structural elements in the TPs can be made and allow a worst-case assessment based on the Threshold of Toxicological Concern (TTC) (step 3). If concerns remain, experiments may be conducted to simulate water treatment (step 4). Because of their complexity and variability, experiments for the simulation of water treatment should focus on prioritized substances of potential concern. The test conditions should be realistic (i.e., close to EU-representative conditions in waterworks) and ozonation and chlorination should be combined with pre- and post-treatment steps, as is normally the case in European waterworks. As a first screening option, we propose to test the toxicity of the reaction mixture. If the treated water shows an enhanced toxicity, further experiments can be conducted to identify and quantify the major TPs (step 5). We propose to define major TPs as substances present at more than 10% of the initially applied test substance. For major TPs, a tiered dietary risk assessment is conducted, starting with the TTC concept, and continuing with toxicity testing of the TP, according to EFSA and ECHA and internationally agreed guidance.

Keywords: Drinking water treatment, Ozonation, Chlorination, Transformation products, Pesticides, Risk assessment

Introduction

Water disinfection is essential to the protection of public health. By removing pathogenic microorganisms responsible for waterborne diseases, it guarantees the microbial safety of drinking water [1]. Chemical oxidation processes are often used for water disinfection. They involve a chemical oxidant, often chlorine or ozone, that deactivates pathogens, and contributes to the abatement of micropollutants [1].

The reaction of the chemical oxidant with organic substances present in the raw water used for drinking water production may lead to the formation of transformation products (TPs) which can be of toxicological concern. Organic substances present in the raw water may be of natural origin [like natural organic matter (NOM)] or

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result from human activities (anthropogenic contaminants such as biocides, industrial chemicals, pesticides, pharmaceuticals, etc.) [2]. While the concentrations of micropollutants, if detectable, are generally in the ng/L or low µg/L range, the concentration of NOM (usually measured as dissolved organic carbon (DOC)) is typically between 0.2 mg/L and more than 10 mg/L [3]. In some cases, the TPs formed during water treatment have been found to be more toxic than the substance(s) initially present in the raw water. The carcinogenic *N*-nitrosodimethylamine (NDMA) for example, is formed during the ozonation of *N*,*N*-dimethylsulfamide (DMS), a metabolite of the fungicide tolylfluanid [4].

A risk–benefit analysis of drinking water treatment still clearly speaks in favor of water disinfection. According to the World Health Organization, "the risks to health from these by-products are extremely small in comparison with the risks associated with inadequate disinfection, and it is important that disinfection efficacy not be compromised in attempting to control such by-products." [1].

The progress in analytical techniques made over the last decades allows the detection of hundreds of micropollutants and their transformation products. As pointed out by von Gunten in 2018, a comprehensive screening of all micropollutants including kinetic and mechanistic studies of oxidation reactions seems unfeasible [5, 6]. Instead, a prioritization is needed and could be achieved using tiered screening methods (see Fig. 1).

For plant protection products (PPPs), TPs formed during water treatment are explicitly mentioned in the EU Regulation prescribing the approval conditions for the placing of a PPP on the EU market: "the residues of PPP […] shall have no immediate or delayed harmful effects on human health […], directly or through drinking water (taking into account substances resulting from water treatment)." [7] However, up to now, no guidance was available on how to address the TPs formed during drinking water treatment. Consequently, information provided by applicants seeking for the approval or renewal of an active ingredient varies and member states responsible for the evaluation of the PPP data package lacked guidance to decide if sufficient information was provided to assess the risk. Recognizing this situation, the European Commission has initiated the development of a new Guidance Document [8]. The primary focus should be on the water disinfection treatment methods of ozonation and chlorination.

The objective of the present paper is to propose a framework for the identification of potential concerns for public health resulting from TPs formed from PPP residues during drinking water treatment. The proposed

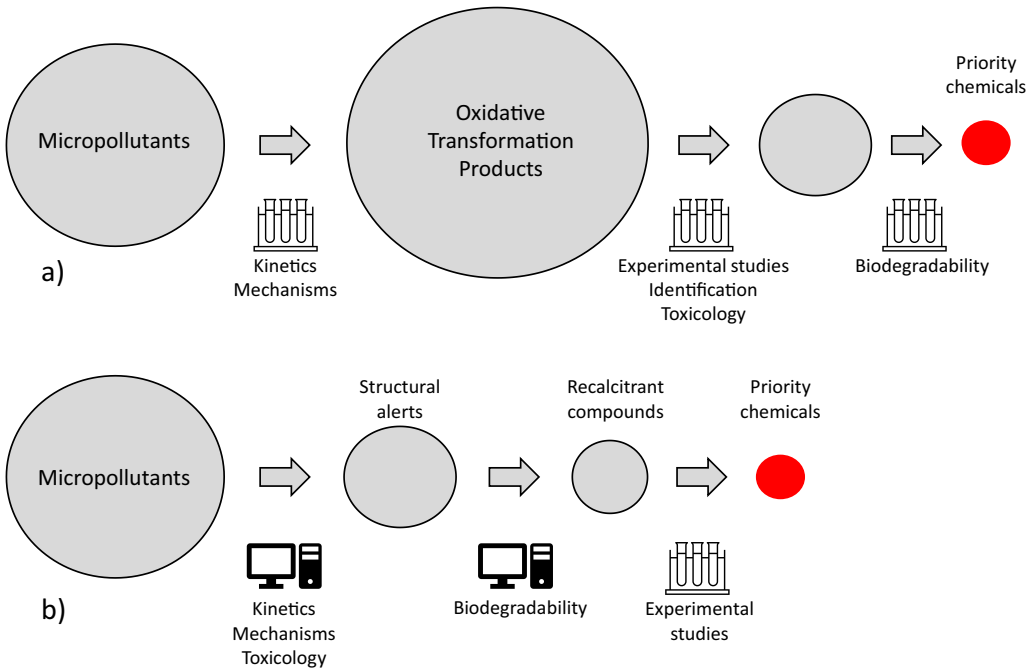


Fig. 1 Approaches presented by von Gunten [5] to assess the large number of TPs. **a** Experimental approach with kinetic and mechanistic studies, toxicological assessment, and elucidation of problematic compounds. **b** In silico assessment of micropollutants by prediction of TPs and potential (eco)toxicological risks. For **b** experimental studies will only be performed with critical compounds (Adapted from [5] with permission from the publisher. Copyright (2018) American Chemical Society)

tiered approach is presented in a schematic way in Fig. 2 and is explained in detail in the following sections.

Tiered approach

Surface water and groundwater are the main sources of raw water for drinking water production in the EU [9]. We hence propose to include in the assessment the PPP active ingredient and the metabolites potentially present in groundwater and surface water (i.e., metabolites included in the residue definition for risk assessment for groundwater and surface water of the active ingredient according to Regulation No. 283/2013 [10]).

Step 1: Exposure assessment

The objective of the exposure assessment is to evaluate concentrations of active ingredients and their respective metabolites present in raw drinking water sources, namely surface water and groundwater. Raw water in this context is defined as water existing in the environment that has not been treated or purified for human consumption. In order to assess raw water concentrations, a stepwise approach for the exposure assessment is proposed based on a dilution factor concept and regional modeling.

Existing approaches to evaluate PPP concentrations in raw water used for drinking water production

Regulatory models to assess the concentration at drinking water abstraction locations Environmental exposure assessment is a mandatory step for the registration of a PPP in the EU [7]. Therefore, predicted environmental concentrations (PECs) in the environmental compartments soil, groundwater, surface water, sediment and air are derived based on conservative scenarios that are considered representative for the EU. For surface water, scenarios represent a single field adjacent to a water body with the primary goal to assess the exposure in the water body (edge-of-field PEC_{sw}) and consequently the risk to aquatic organisms under worst-case conditions.

On national level in the Netherlands, a regulatory concept (DROPLET) assesses the concentrations of PPPs at drinking water abstraction locations originating from surface water, i.e., considering such edge-of-field PEC_{sw} values [11]. DROPLET evaluates concentration dilution along the way from the edge-of-field water body to drinking water abstraction points. Four aspects driving dilution in surface water bodies are: (1) the ratio between the crop area over the entire intake area; (2) the market share of the PPP, reflecting that the compound is not used on the entire crop area; (3) the variability in application timing; (4) degradation and volatilization on the way from the edge-of-field watercourse to the abstraction points. It assumes a worst-case scenario that all agricultural land is connected directly to surface water bodies.

The DROPLET concept is exclusively designed for the Netherlands considering specific characteristics of agricultural land use, water network, surface water catchments, climatic conditions, and water abstraction types. Between and even within different EU member states a large variety of these ecohydrological characteristics may exist, which affects itself, volume distribution, and methods for groundwater and surface water abstraction [12]. On this account, the DROPLET concept serves as a starting point, but requires adaptation and extension of impact factors before applying to other surface water catchments in the EU.

Literature studies on the estimation of PPP concentrations in raw water Data on PPPs concentrations in surface water and groundwater mainly originate from two types of sources:

1. *Direct measurement by monitoring data* (e.g., [13–16]). Monitoring data can provide valuable information on the actual occurrence of a compound of interest in surface waters or groundwaters used for drinking water production. Extensive monitoring data on the chemical status of surface water and groundwaters and especially the occurrence of PPPs and their metabolites are available in most EU member states as required by the Water Framework Directive [17]. It should also be mentioned that the regulation 1107/2009 requires the applicant to collect, evaluate and submit all available monitoring data of the PPP active ingredient and its metabolites with each renewal of authorization of the PPP. These data can be used to evaluate the actual occurrence of a substance of interest in groundwater and surface waters. Moreover, the monitoring data may support calibration and validation methods for modeling approaches at catchment level. For example, the GRDC [18] offers global measured discharge data at daily and monthly temporal scale, which may be used, e.g., in the Soil and Water Assessment Tool (SWAT) [19] to calibrate and validate hydrological fluxes (e.g., [20]).
2. *Modeling approaches*. Modeling approaches for surface water often involve catchment scale modeling, such as the pesticide transport model for surface water bodies [21], and SWAT for the simulation of concentrations in surface water watersheds [22–24]. For groundwater, the evaluation of the vulnerability to PPPs includes indicator or index methods (e.g., [25–27]) or process-based or physically based numerical models. These models simulate the physi-

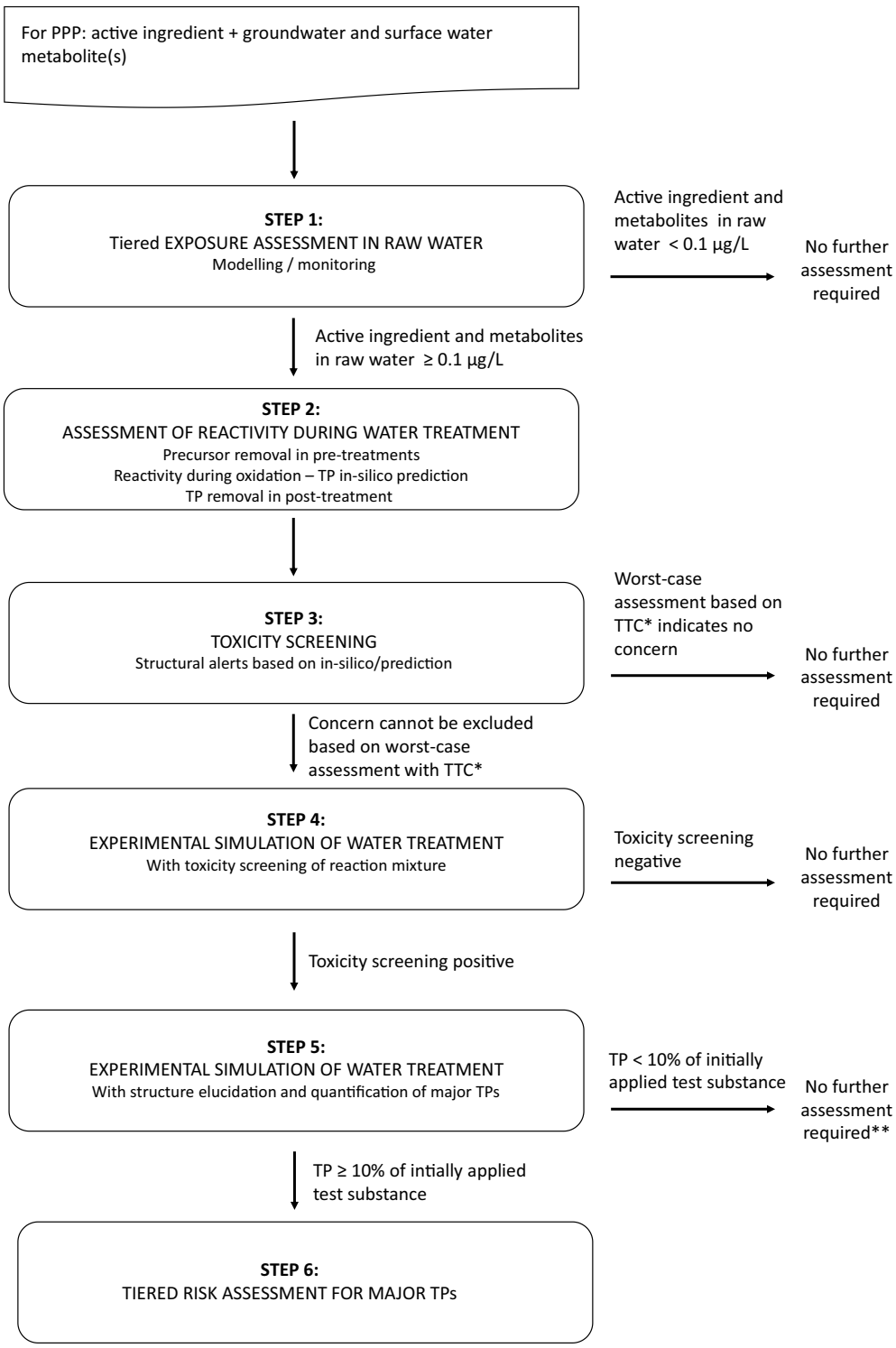


Fig. 2 Proposed approach to assess impact of water treatment on residues of pesticides and their metabolites

cal, chemical, and biological environmental fate of the PPPs from the land surface through the vadose zone [28]. For both surface water and groundwater, the application of geospatial analysis or the combination of modeling and geospatial analysis has become more popular in recent years [28].

A proposal for a stepwise exposure assessment for the EU

In this work, we focus on surface water as a raw water source for drinking water production. The surface water compartment serves as a first example of concept and methodology. In principle, the concept can be transferred to groundwater as well, i.e., starting with regulatory PEC_{gw} values and consideration of dilution factors until the point of abstraction [29] by additionally taking geometric configuration of groundwater aquifers into account.

In order to assess surface water as a raw water source for drinking water, an identification of surface water catchments and a classification of their vulnerability in the EU is required. This can be achieved by identifying and quantifying the driving factors leading to dilution from the edge-of-field to drinking water abstraction locations. A stepwise approach for the exposure assessment is proposed here to derive these driving factors:

- At exposure assessment step 1, a geospatial analysis to quantify each individual impact factor affecting overall dilution for all surface water catchments in the EU. A dilution factor concept is introduced, allowing the quantification based on newly generated datasets at EU scale—surface water catchments with high-resolution (100 m grid cell) [30]. This allows the identification of potentially vulnerable drinking water catchments based on a vulnerability ranking (e.g., defining a percentile based on the cumulative frequency distribution for a certain land use). By doing so, all EU surface water catchments from a holistic point of view are assessed, by using a general concept while considering variabilities between catchments and climatic characteristics. This can be considered as a screening process to exclude catchments or areas that are not potentially vulnerable for certain conditions.
- At exposure assessment step 2, targeted regional modeling analysis is used to derive more realistic generic dilution factors in those potential vulnerable drinking water catchments identified from step 1.
- At exposure assessment step 3, compound-specific and use-dependent concentrations in raw water at the drinking water abstraction locations can be derived by means of modeling in catchments identified at step 2.

Dilution factor (DF) concept This concept is based on the DROPLET approach. Some additional factors, however, are considered for a proper characterization of potential drinking water intake areas on EU scale. In contrast to DROPLET, the market share factor was neglected. This concept has been presented at SETAC by Gebler et al. [30].

The concentration at abstraction locations can be calculated as:

$$PEC_{abstr.location} = PEC_{edge\text{-}of\text{-}field}/DF, \quad (1)$$

with $PEC_{abstr.location}$ is the predicted concentration at potential abstraction locations (virtual or real-world); and $PEC_{edge\text{-}of\text{-}field}$ is the predicted surface water concentration at the edge-of-field.

The dilution factor is defined as:

$$DF = f_{agrLU} * f_{hydrology} * f_{connectivity} * f_{appTiming} * f_{x}, \quad (2)$$

where f_{agrLU} is the factor reflecting upstream agricultural land use (e.g., arable crops, permanent crops) potentially taken into account for PPP application; $f_{hydrology}$ is the factor accounting for variability, resp., potential availability of surface water within different land cover in a catchment. As hydrological characteristics between agricultural and other areas (e.g., grassland, forest) are different between climate zones and landscapes, this factor is not considered in the DROPLET concept; $f_{connectivity}$ is the factor accounting for the connectivity of agricultural fields to the adjacent surface water bodies and the stream network; $f_{appTiming}$ is the factor accounting for typical application pattern and periods; f_{x} represents any other potential factors (e.g., dissipation, retention times, abstraction type, etc.).

To derive the individual impact factors, we used the EU public datasets listed in Table 1.

The stepwise approach for the exposure assessment to derive dilution factors

- **Exposure assessment step 1—geospatial analysis**

  The state-of-the-art EU-wide surface water catchment map [30] (Fig. 3) can be spatially overlayed with each impact factor (from Eq. (2)) i.e., land use, hydrology and connectivity derived based on the data listed in Table 1. First, land use is assessed to derive dilution factors for a crop or crop class

Table 1 Datasets used for the derivation of impact factors for the generic geospatial distributed dilution factor

Data source	Dataset includes	Resolution	Temporal coverage	To derive	References
CCM2 Database—EU Water Framework Directive	River basin networks and catchment boundaries	100 m	1975–1999	Upstream agricultural land use f_{agrLU}	[31, 32]
CORINE Land Cover (CLC) 2018	Agricultural and non-agricultural land use types	100 m	2018	Upstream agricultural land use f_{agrLU}	[33]
WorldClim2.0 database—MARS Geodatabase	Mean annual precipitation	1 km	1970–2000	Precipitation $f_{hydrology}$	[34]
Global aridity index and Potential Evapotranspiration Climate Database v2	Global aridity index, potential evapotranspiration	1 km	1970–2000	Actual evapotranspiration for $f_{hydrology}$	[35–37]
Open Street Map	Country-level surface water types, water streams, etc.	1 m	2020	Connectivity factor $f_{connectivity}$	[38]

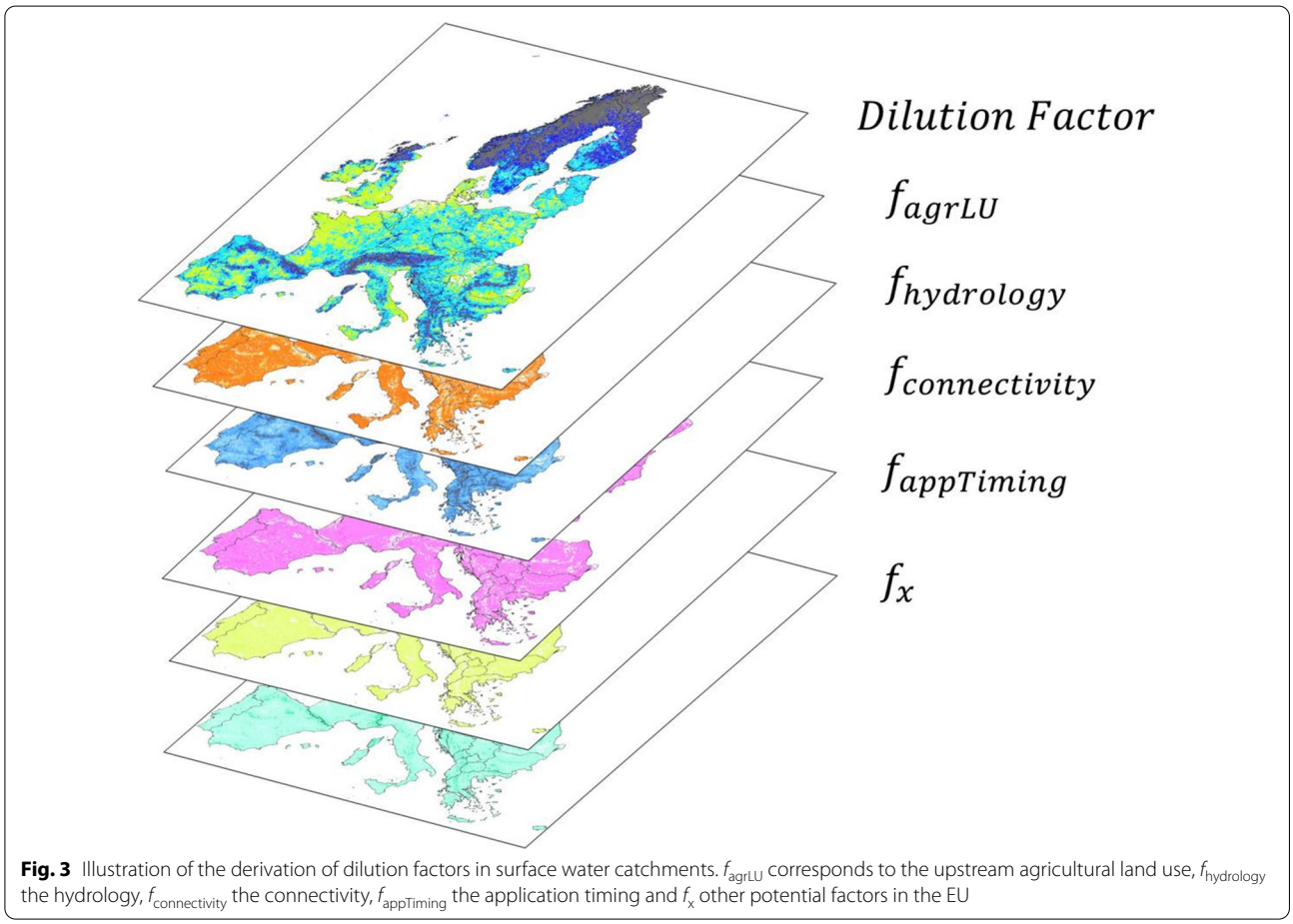


Fig. 3 Illustration of the derivation of dilution factors in surface water catchments. f_{agrLU} corresponds to the upstream agricultural land use, $f_{hydrology}$ the hydrology, $f_{connectivity}$ the connectivity, $f_{appTiming}$ the application timing and f_x other potential factors in the EU

for all surface water catchments in the EU (e.g., fruit and berry plantations, see Fig. 4a). By adding more impact factors, the dilution factor gets larger. This leads to a shift of the cumulative distribution function (Fig. 4b) towards the right as indicated by the blue line (dilution factor including land use and hydrology), whereas the yellow line indicates land use only. Then, based on the *N*th percentile of the cumulative distribution of this dilution factor (Fig. 4b), potential vulnerable drinking water catchments with dilution factors smaller than this percentile can be identified (Fig. 4c), for illustration purposes the 10th percentile is used.

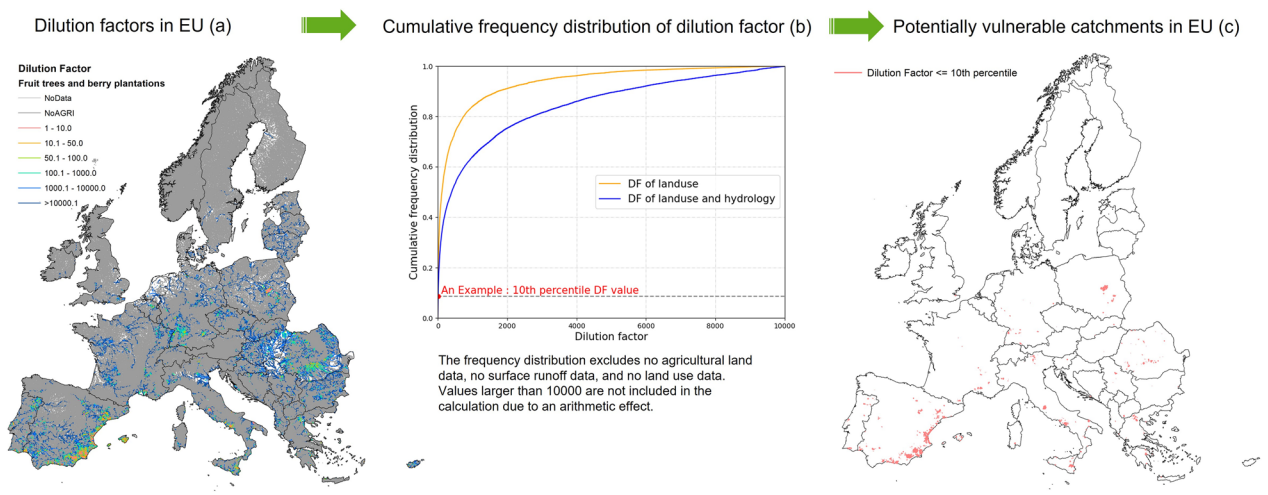


Fig. 4 Identification of potential vulnerable drinking water catchments based on DF distribution of a crop class. **a** Shows dilution factors considering crop type fruit trees and berry [equivalent to f_{agrLU} in Eq. (2)] and hydrology factor [equivalent to $f_{hydrology}$ in Eq. (2)]. **b** Illustrates the cumulative frequency distribution of dilution factors from **a**. **c** Indicates the corresponding potential vulnerable drinking water catchments in EU identified by using exemplary the 10th percentile dilution factor value from **b**

- **Exposure assessment step 2—regional modeling** After identification of potential vulnerable catchments for the crop types of interest, e.g., fruit trees and berry (Fig. 4c), quantification of realistic dilution factors can be performed by using the regional modeling approach. The SWAT model is proposed to be used as it has been recognized as one of the top three models that are most appropriate for watershed-scale simulation of pesticides concentrations [39]. Li et al. [40] investigated potential dilution factors in a vulnerable drinking water catchment in Spain—the Ebro catchment—using the SWAT model. Other examples include the application of the SWAT model to simulate the reduction of PPPs in a surface water catchment—Drentsche Aa in the Netherlands [24, 41]. Typical dilution factors derived from regional modeling would range between 10^2 and 10^6, however, largely dependent on catchment characteristics, topography, hydrology, seasonal flow and climatic conditions.

Conclusions and outlook

Our methodology focuses on predicting PPP concentrations at drinking water abstraction locations using surface water as a source. A stepwise approach for the exposure assessment is proposed:

- Step 1: geospatial analysis is used to derive generic dilution factors in surface water catchments in the EU, including a vulnerability ranking. Further investigation into the connectivity factor and application timing is still required.
- Step 2: regional modeling is applied to derive more realistic, though generic, dilution factors in the potential vulnerable drinking water catchments identified from exposure assessment step 1.
- Step 3: compound-specific and use-dependent concentrations at drinking water abstraction locations can be derived at the regional level. This requires an extension of current methodology to include all relevant entry pathways for PPP exposure (e.g., drift) required in this landscape level framework.

Using cumulative distribution functions allows for appropriate selection of potentially vulnerable drinking water catchments and needs to be investigated further for regulatory usage. The selection procedure is important, particularly, if one of the targets for guideline development is the generation of representative drinking water scenarios. At regional modeling level it is important to calibrate these scenarios in order to reduce modeling uncertainties. Besides long-term hydrological discharge and corresponding weather data, surface water monitoring data are important means for this.

The stepwise approach for the exposure assessment, as outlined here, follows basic principles already considered in the regulatory framework of PPPs: from a conservative to a more realistic assessment. Therefore, it is recommended to embed such a stepwise exposure assessment approach in guideline development. In combination with

a trigger level, e.g., the EU 0.1 µg/L trigger level already established for active substances and relevant metabolites in drinking water [42], a screening procedure can be established. Compounds below this trigger level require no further evaluation on their reactivity during water treatment processes.

Step 2: Reactivity assessment (oxidation and other treatment steps)

Substances potentially present in the raw water used for drinking water production in concentrations ≥ 0.1 µg/L (see step 1) are examined for their reactivity during water treatment. The objective of the reactivity assessment is to evaluate if harmful TPs are expected to be formed during oxidation and be present in the finished water after post-treatment steps.

The reactivity of organic compounds during oxidation and the formation of TPs has been the topic of numerous scientific publications in the last decades. This abundant scientific literature sheds light on the reactivity of individual functional groups as well as typical reaction mechanisms and can be used to predict, to a certain extent, the structural elements that can be expected in the TPs [5]. In step 2, chemical structures of the substances potentially present in the raw water are investigated with regard to the potential formation of harmful TPs during oxidation, especially ozonation and chlorination ("Reactivity during oxidation" section).

Oxidation is usually not performed alone but is commonly included in a more complex treatment train, including pre- and post-treatment steps, each contributing to the removal of chemicals [1]. Abatement of precursors during pre-treatment steps and TPs during post-treatment steps should be considered for a realistic representation of the situation in drinking water treatment plants ("Reactivity during other treatment steps" section). Note that these additional treatment steps are often implemented independently of the presence of PPP residues in the raw water.

Reactivity during oxidation

Reactions of organic compounds during ozonation and chlorination During ozonation, organic compounds may react directly with ozone or with OH radicals formed by the decomposition of ozone. While ozone selectively attacks electron-rich moieties (e.g., double bonds, activated aromatic rings, neutral amines and thioethers), the highly reactive OH radicals are less selective. As both species are present during water treatment, reactions with ozone and OH radicals are likewise relevant.

Chlorination commonly leads to transformation of electron-rich sites (e.g., activated aromatic rings, double bonds and heteroatoms/bonds including deprotonated amines, thioethers and amides) via electrophilic attack. Under typical water treatment conditions, the reactive chlorine species are distributed between hypochlorous acid (HOCl) and hypochlorite (OCl^-), based on the p*K*a of 7.5. With few exceptions, HOCl is considered the main oxidant species involved in the chlorination of organic compounds [43]. There are three kinds of reactions of hypochlorous acid with organic compounds: (i) oxidation reactions, (ii) addition reactions to unsaturated bonds, and (iii) electrophilic substitutions at nucleophilic sites.

Assessment of reactivity based on the existing scientific literature Although the actual reaction outcome depends on several variables (for example pH, oxidant concentration, water matrix) the prediction of possible transformation pathways for micropollutants during ozonation or chlorination, and the deduction of possible TPs is possible for a number of drinking water pollutants with common structural motifs. Certain functional groups, common to numerous micropollutants (e.g., phenols, olefins, and amines, including anilines, or heterocyclic amines), have already been intensively studied ([44–49] to cite a few). This abundant scientific literature provides information on the reactions of individual functional groups during oxidation and may be used to predict the TPs of micropollutants with similar structural elements. As a first step to evaluate the potential formation of harmful TPs we thus propose to use the existing scientific literature to gain information on possible reactions of the functional groups present in molecules of interest. Literature data can additionally be used to populate a chemical structure database with reaction schemes for proven transformations. Such a database of oxidation reactions could facilitate the search for published data and could be an asset for reaction prediction and the development of in silico pathway prediction tools.

To illustrate how literature data can be used to predict the reactivity of a micropollutant, the case of the aniline moiety in sulfamethoxazole may serve as an example. The reactivity of aniline during ozonation has been studied by Tekle-Röttering [50]. The authors conducted batch experiments at bench-scale investigating the kinetics, stoichiometry, and product formation for the reaction of ozone with several anilines, bearing different substituents. In case of aniline, ortho- and para-hydroxylated and 2-amino-5-anilino-benzoquinon-1,4-anil were identified as main transformation products. As minor TPs, nitrobenzene, nitrosobenzene, and azobenzene, resulting from the ozone attack at the nitrogen, were identified (Fig. 5a).

The reaction of sulfamethoxazole (Fig. 5b) with ozone in aqueous solution has been investigated by several authors [51–55]. The TPs identified in these works are in

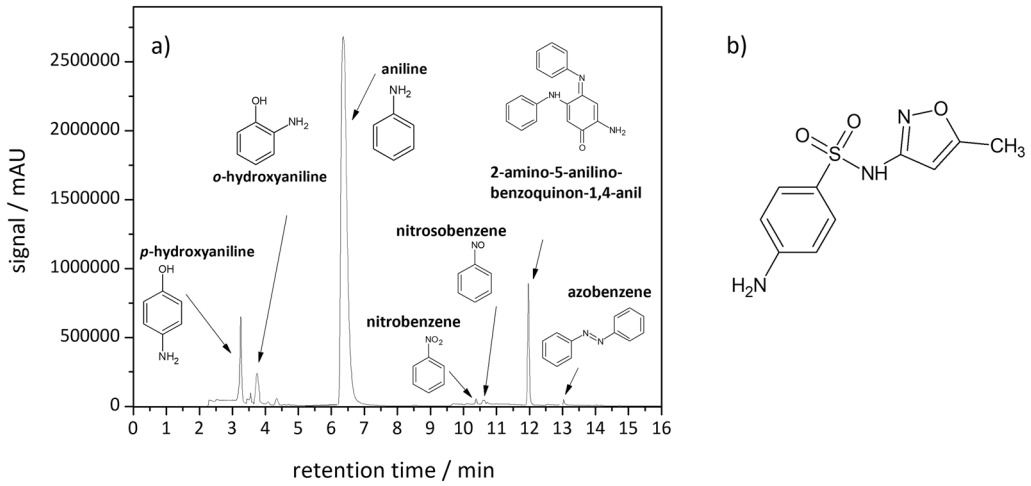


Fig. 5 **a** Chromatogram after ozonation of aniline (without OH radical scavenger). **b** Chemical structure of sulfamethoxazole (Adapted from [50], Copyright (2016), with permission from Elsevier)

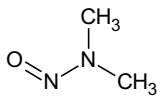


Fig. 6 Chemical structure of *N*-nitrosodimethylamine (NDMA)

good agreement with the work of Tekle-Röttering. They confirm that the reaction of ozone on the aniline moiety of sulfamethoxazole proceeds via ozone attack on the aromatic ring, leading to the addition of a hydroxyl group to the aniline ring, and an electrophilic attack at the aromatic amino group, leading to nitrobenzene and nitrosobenzene. In the case of sulfamethoxazole, the formation of a corresponding 2-amino-5-anilino-benzoquinon-anil derivative is not expected because of steric hindrances.

With recent developments in quantum chemical modeling and increased computation capacity, in silico prediction tools may develop into a viable alternative to predict the fate of micropollutants during oxidation. Quantum chemical computations can be used to predict reaction kinetics as well as to investigate reaction mechanisms and the formation of TPs [56, 57]. Such methods have, for example, already been successfully applied to rationalize the formation of NDMA from *N*,*N*-dimethylsulfamide during ozonation [58].

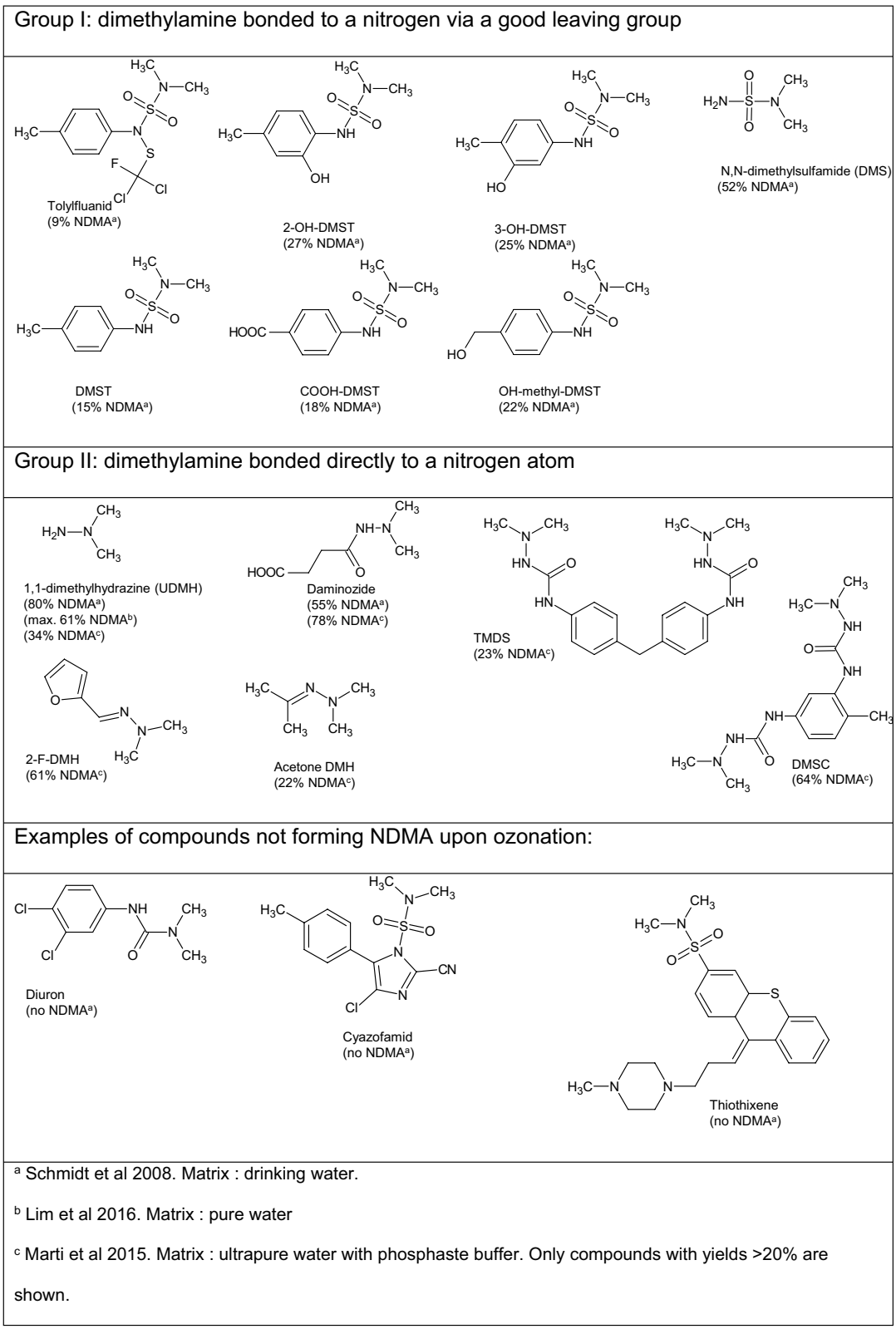
Formation of nitrosamines Because the formation of nitrosamines during water treatment has been regarded with particular concern and extensively investigated, the following section examines more specifically the formation of nitrosamines during oxidation. Numerous peer-reviewed publications cover *N*-nitrosodimethylamine (NDMA, Fig. 6), making it the most studied nitrosamine.

Ozonation High levels of NDMA were observed after ozonation of wastewaters or highly contaminated surface waters. The currently most accepted NDMA formation pathway during ozonation at neutral and alkaline conditions involves the condensation of dimethylamine with hydroxylamine to unsymmetrical dimethylhydrazine (UDMH), which is further oxidized to NDMA [59]. Hydroxylamine may derive from the oxidation of ammonia or prior decomposition of nitrogenous organic precursors.

The abundant scientific literature investigating the formation of NDMA during ozonation in conditions relevant for drinking water production allows the identification of possible NDMA precursors and their allocation into two groups (Fig. 7).

During ozonation, high NDMA yields were observed for a limited subset of compounds. Compounds with dimethylamine bonded directly to a nitrogen atom (Group II in Fig. 7) or separated with a good leaving group (Group I in Fig. 7) were seen to form NDMA with significant molar conversion yields [59–61]. In case of UDMH and daminozide, it was suggested that ozone mainly attacks the unsubstituted nitrogen of UDMH or the nitrogen neighboring the carbonyl group of daminozide, forming an ozone adduct which decomposes via homolytic and heterolytic cleavage, directly yielding NDMA [4, 61].

Compounds containing dimethylamine but no additional nitrogen adjacent to the dimethylamine functional group may form NDMA upon ozonation but the



[a] Schmidt et al 2008. Matrix : drinking water.

[b] Lim et al 2016. Matrix : pure water

[c] Marti et al 2015. Matrix : ultrapure water with phosphaste buffer. Only compounds with yields >20% are shown.

Fig. 7 Precursors investigated for NDMA formation during ozonation of drinking water and molar NDMA conversion rates [4, 60, 61]

yields are < 0.01% [60]. More generally, in conditions relevant for drinking water production, no formation of NDMA was observed during ozonation of secondary amines lacking an adjacent second nitrogen atom [62].

The mechanism for NDMA formation from the metabolites of tolylfluanid was discussed in detail [4, 63] and rationalized using quantum mechanics [58]. The linkage of two nitrogen atoms by a good leaving group (an atom or group of atoms which easily cleaves from the rest of the molecule, such as SO_2), promoting coupling and rearrangement, was proposed as a prerequisite, providing an explanation for the absence of NDMA formation with thiothixene (lack of a second nitrogen), cyazofamid (tertiary second nitrogen) and diuron (carbamide linkage) (Fig. 7). Additionally, one of the nitrogen atoms should be able to form, as reaction intermediate, a primary amine that can easily be halogenated and consecutively deprotonated. During water treatment, the halogenation step is facilitated by the oxidation of naturally occurring bromide to hypobromous acid during ozonation (catalytic effect).

In conclusion, the number of precursor substances that are responsible for significant NDMA yields upon ozonation for drinking water production is limited [4, 60]. The structural elements leading to the formation of nitrosamines in significant yields are quite well characterized and involve dimethylamine bonded directly to a nitrogen atom or separated with a good leaving group.

Chlorination/chloramination An enhanced NDMA formation during chloramination over plain chlorination has frequently been observed [64–68]. The mechanisms of NDMA formation during chlorination have not been exhaustively investigated. However, nitrosation of free dimethylamine and oxidation of UDMH [59, 69, 70] have been proposed. During chloramination, NDMA formation pathways involving the nucleophilic reaction of dichloramine with dimethylamine yielding chlorinated UDMH, followed by subsequent oxidation by dissolved oxygen, have been suggested [71, 72]. As chloramines may be released due to the decomposition of nitrogenous organic compounds by chlorine oxidation [66, 67, 73], the UDMH-pathway may also play a role during chlorination. The UDMH-pathway involving free dialkylamines has been proposed for the NDMA formation during chlorination and chloramination of dimethyl- and diethyldithiocarbamate [66, 67], diuron [65, 67] and various tertiary and quaternary *N*,*N*-dimethylamines [73].

During chlorination of various compounds carrying a *N*,*N*-dimethylamino group, the chemical neighborhood was found to significantly influence NDMA formation rates and yields. Low yields were observed with the *N*,*N*-dimethylamino moiety bound to electron withdrawing groups, whereas higher yields were determined with the *N*,*N*-dimethylamino moiety being part of a tertiary aliphatic amine [64, 74]. Among several investigated tertiary amines, enhanced NDMA-formation yields were observed with ranitidine [73]. This observation has been generalized for homologous compound, in which the *N*,*N*-dimethylamino moiety is linked via a methylene bridge to an aromatic ring [75]. In case of ranitidine chloramination, a unique pathway without the requirement for free DMA or UDMH has been suggested [68]. Nucleophilic attack of the DMA-moiety of ranitidine on monochloramine is suggested to lead to a cationic dimethylhydrazinium intermediate via *N*–*N*-coupling and chloride elimination. Through a cascade involving deprotonation, oxidation by dissolved molecular oxygen and hydrolytic cleavage, NDMA and a (hydroxymethyl) furan derivative were released.

Disinfection by-products (DBPs) The denomination DBP is commonly used to designate oxidation products of low molecular weight, such as trihalomethanes (THMs) or haloacetic acids (HAAs). DBPs are formed to a large extent from the reaction of NOM present in the raw water [5, 43]. Due to the low concentrations of micropollutants compared to NOM (ng/L to low µg/L range for micropollutants compared to mg/L range for typical DOC concentrations [76]), DBPs mainly originate from NOM [43]. As the formation of DBPs during water treatment is commonly not related to the presence of specific micropollutants in the raw water but to a much larger extent from natural substances, DBPs are not in the scope of this study. Regulatory thresholds are defined for certain classes of DBPs. The Drinking Water Directive for example sets a parametric value for THM at 100 µg/L (sum of THMs) [42].

Reactivity during other treatment steps

Depending on the local quality of the raw water and following the so-called multiple-barrier principle, several treatment steps are usually combined to ensure the highest level of safety for the finished drinking water [1, 3, 44, 77]. The widespread implementation of pre- and post-treatments (before and after the oxidation step) has been fostered by the need to reduce the occurrence of harmful DBPs, known since the 70 s to be formed from NOM during oxidation [78, 79]. Pre-treatments primarily aim at reducing the concentration of NOM and other organics precursors of DBPs, while post-treatment aims at removing DBPs potentially formed.

In case of ozonation, post-treatments are also implemented to improve the biostability of the water. The reaction of ozone with dissolved organic matter leads to the formation of numerous small oxygen-rich molecules

(such as carboxylic acids, aldehydes, or ketones) commonly referred to as assimilable organic carbon (AOC) or biodegradable organic carbon (BDOC). As the presence of these easily biodegradable compounds in the water can promote the regrowth of microorganisms in the distribution system, their removal is necessary and is commonly achieved by implementing biological post-treatments after oxidation [44, 80], such as filtration with activated carbon or biological sand filtration.

Pre-treatment before oxidation Pre-treatment processes commonly involve coagulation/flocculation/decantation, filtration, or pre-oxidation (pre-ozonation/pre-chlorination):

- **Coagulation/flocculation/decantation** is primarily implemented to reduce the water turbidity by removing suspended particles, but has also been shown to contribute to the removal of micropollutants. The main mechanism for micropollutants removal during coagulation/flocculation is via adsorption to the organic material present in the raw water and flocs followed by their removal by sedimentation. Removal efficiencies correlate with the hydrophobicity and are usually low to moderate for semi-polar substances like pesticides [81, 82].
- **Sand filtration**
  The removal of micropollutants in sand filters has been associated with biodegradation along with the growth of microorganisms on the surface of the sand sustained by the steady flux of nutrients. Removal efficiencies of micropollutants significantly vary from no removal to almost complete removal [81].
- **Pre-oxidation** steps, consisting of pre-oxidation with ozone or chlorine, have been described as the most efficient treatment for the reduction of micropollutants before oxidation [77, 83, 84].
- **Riverbank filtration and artificial groundwater recharge**
  When river water is abstracted for drinking water production, underground passage based on riverbank filtration or artificial groundwater recharge, is often applied. In Germany for example, approximately 16% of the drinking water is produced from bank filtrate or infiltrate [85]. Today almost all waterworks using water from large rivers employ a combination of treatments steps, as part of multiple-barrier systems (see Fig. 8) [85–88].
  Riverbank filtration and artificial groundwater recharge demonstrated to be excellent options for the removal of micropollutants [85]. Elimination proceeds via adsorption and biological transformations. For hydrophobic substances, adsorption to aquifer solids plays a major role in elimination. For polar substances, adsorption plays a lesser role, but the retarded transport through the aquifer enables a prolonged availability to microorganisms, thus promoting biodegradation.

Post-treatment after oxidation

- **Activated carbon filtration**

  Activated carbons are able to adsorb multiple organic substances, micropollutants as well as NOM. The removal of substances by activated carbon is primarily due to adsorption but biodegradation also plays a significant role. The activated carbon indeed provides a favorable surface for the growth of microorganisms, making biodegradation a relevant mechanism in the removal of organic compounds [89].
- **Sand filtration**
  A comprehensive study on the fate of ozonation TPs during biologically active sand filtration has recently been published by Gulde et al. [80]. The authors investigated the oxidation of 51 micropollutants during ozonation. They identified the TPs formed during ozonation and investigated their abatement in a post-treatment by a biological sand filter. They observed that approximately 20% of the TPs detected after ozonation were abated by the biologically active sand filter, while 76% were found to be stable and 5% of new TPs were formed during filter passage. Removal in the biological sand filter was found to depend on the functional groups present in the TPs. Degradable TPs were found to frequently possess aldehyde, carbonyl, alcohol, carboxylic acid or amide groups. These results were generally in line with the theoretical study performed by Hübner et al. [90], investigating the persistence of TPs formed during ozonation.

Addressing the question of TPs formed during water treatment requires consideration of the entirety of treatment steps. Pre-treatments before oxidation reduce the concentration of precursors reaching the oxidation step. Post-treatments after oxidation reduce the concentration of TPs potentially formed.

Step 3: Toxicity screening based on TTC concept

With the information resulting from step 1 (i.e., the estimated concentrations of PPP active ingredients and metabolites in the raw water for drinking water production), and the information from step 2 (i.e., predicted TPs and their removal in pre- and post-treatment steps in waterworks), estimation of worst-case concentrations of predicted TPs in finished water can be made. However, at this point no information is available on the conversion

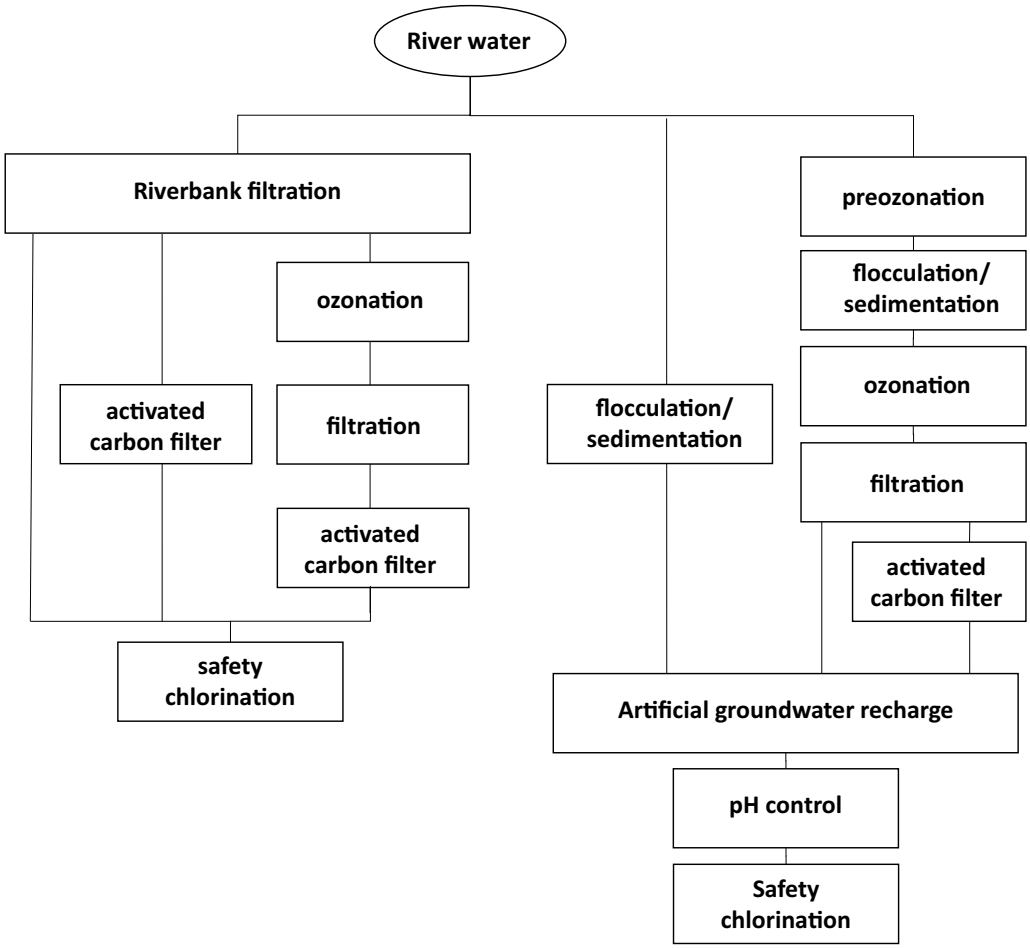


Fig. 8 Typical treatment process in Germany including riverbank filtration and artificial groundwater recharge (adapted from [85], with permission from the copyright holders, IWA Publishing)

rate of the active ingredient/metabolite to TP(s). As multiple TPs are generally formed, a conversion rate of 100% seems inappropriate. Instead, a conversion rate of 80% could be used. This corresponds to the upper range of conversion rates, as observed for example with daminozide (see "Reactivity during oxidation" section). A conversion rate of 80% is a very worst-case assumption but nevertheless can be used to conduct a preliminary toxicity screening. The proposed assessment scheme is in general alignment with similar approaches used for other regulatory areas like food contact materials and medical devices. The process is depicted in Fig. 9.

The assessment is based on the concept of Threshold of Toxicological Concern (TTC) [91]. The TTC is intended to provide a health-protective approach in situations where it is not feasible to acquire chemical-specific data (e.g., data poor substances, impurities and breakdown/reaction products in food additives, trace contaminants in food and water) [92, 93], where evaluation of a large number of compounds with low exposure is required (such as flavoring substances), in prioritization of large numbers of compounds where resources are limited (e.g., contaminants in surface water) this is also the case for the predicted TPs.

In a first step (hazard screening, Box 1), the substances/structures, for which the TTC concept cannot be applied shall be identified [94]. Substances not represented in the database underlying the TTC concept are inorganic substances, proteins, nanomaterials, radioactive and organosilicon substances and metals. Further, for some high potency chemicals (aflatoxin-like, azoxy- or *N*-nitroso substances) steroids, and substances with a potential for bioaccumulation (including polyhalogenated-dibenzo-dioxins, -dibenzofurans or -biphenyls) the TTC concept is not applicable. If such compounds might be formed, experimental data would be required, and the assessment would progress to Step 4 in Fig. 2.

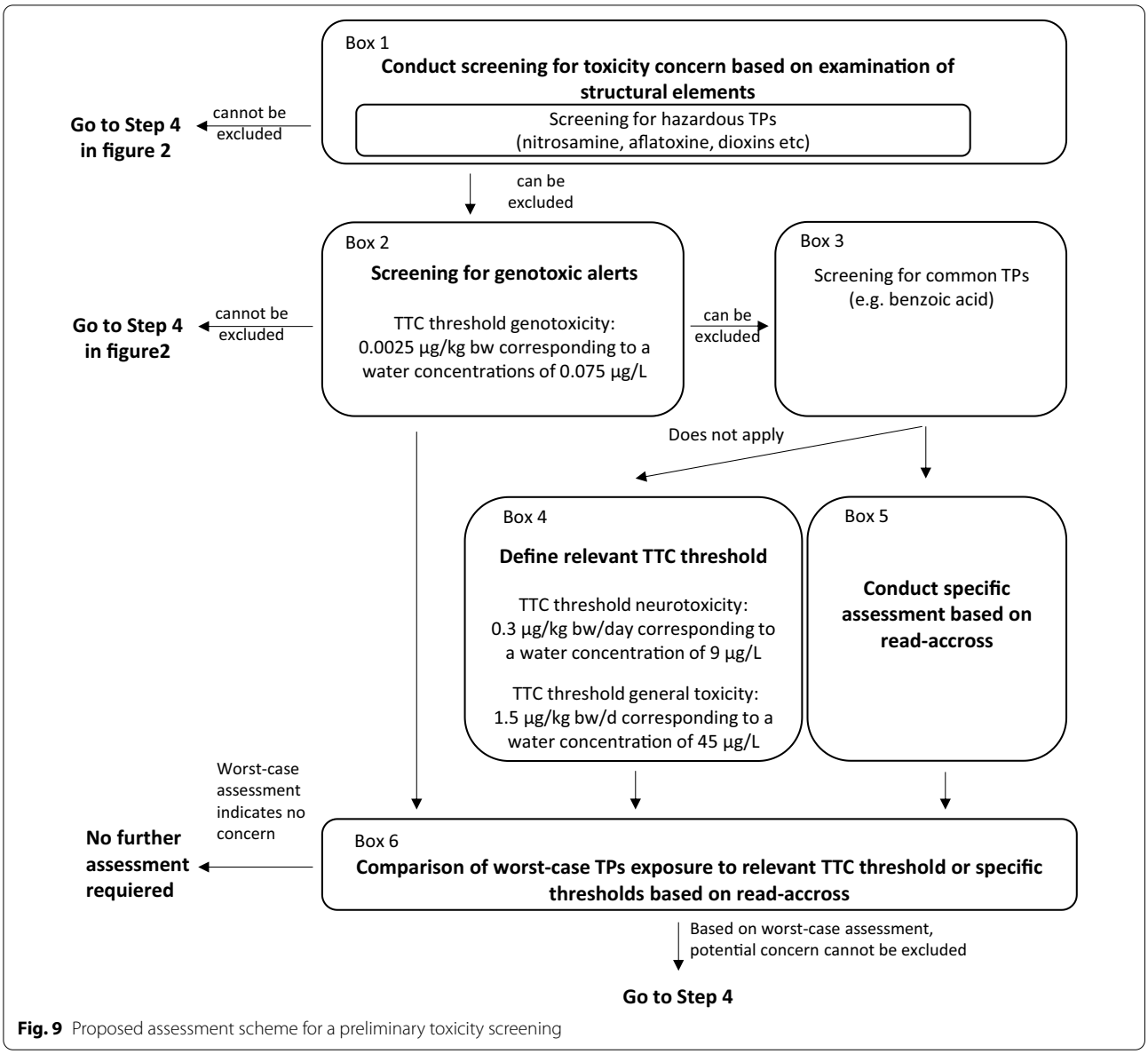


Fig. 9 Proposed assessment scheme for a preliminary toxicity screening

In the next step (Box 2) the formation of genotoxic alerts is evaluated after assessing if compounds exceed the TTC value for genotoxicity. The TTC value of 0.0025 µg/kg body weight (bw) corresponding to an allowable water concentration of 0.075 µg/L (bw of 60 kg, drinking water consumption of 2 L with 100% allocation) can be considered a safe threshold [94]. If such compounds might be formed, experimental data would be required, and the assessment would progress to Step 4 in Fig. 2.

Otherwise, the assessment proceeds to the screening for structural elements commonly formed through water treatment (Box 3). Water treatment and especially ozonation and chlorination generally result in a decrease of the molecular weight of the organic compounds present in the raw water [44], and it can be expected that a significant fraction of the TPs resulting from water treatment will be common to several precursors (micropollutants, but also, natural organic substances). Identification of common substructures would be based on chemical knowledge and literature data. Structures could for example include formation of benzoic acid and derivatives as described for water treatment of humic acid [95]. Ideally, common TPs and substructure fragments would be collected into a peer-reviewed database. Currently, no such database is available. To facilitate the process, it would be recommended to create such a repository, including not

only transformation products, but rate of formation and ideally exposure information from different sources.

Typical structural elements can easily be encoded into substructure fragments and included into a number of in silico tools like Chemotyper or the OECD toolbox to allow for easy screening, similar to what is performed in QSAR systems for genotoxicity.

If no common TP structures can be identified, the assessment would move forward to Box 4 with an assessment of the predicted exposure against the relevant TTC value. For compounds containing structural elements of neurotoxic concern, the respective TTC values are 0.3 µg/kg bw/d corresponding to a water concentration of 9 µg/L. For compounds containing no structural alert, the TTC values depending on the Cramer Classes would apply. In case of Cramer Class III, the respective value is 1.5 µg/kg bw/d corresponding to a water concentration of 45 µg/L.

In case a common TP element/compound is identified, the evaluation moves forward to a compound-specific assessment based on read across (Box 5). This would entail the evaluation of the toxicity database and evaluation of the impact on the overall exposure burden to which the TP formed would contribute.

In each of the assessments in Box 2, Box 4 and Box 5 a comparison of the toxicological thresholds against a worst-case exposure scenario is performed (Box 6). If no concern is identified, no further testing is required and the assessment stops. In case the evaluation cannot exclude a concern, the assessment would progress to Step 4 in Fig. 2.

Step 4: Experimental assessment—laboratory-scale simulation of water treatment and toxicity testing of reaction mixture

If the worst-case assessment performed in Step 3 identified a concern, experimental investigations may be necessary to further characterize the potential risk. Experimental investigations consist of a laboratory-scale simulation of water treatment (see "Laboratory-scale simulation of water treatment" section).

Before proceeding to the structure elucidation and quantification of individual TPs, we propose, as a first screening option, to conduct toxicity tests on the reaction mixture obtained from the lab-scale simulation of water treatment (see "Toxicity screening of reaction mixture obtained in the laboratory-scale simulation of water treatment" section).

Laboratory-scale simulation of water treatment

Experimental conditions River water and groundwater are the main raw water resources used in Europe with an almost even split between both resources [96]. Due to the influence of pH, alkalinity and dissolved NOM, the ratio of ozone to OH radicals can be vastly different depending on the water matrix [97]. The different reaction behaviors of ozone in comparison to OH radicals can influence the transformation pathway. Consequently, the same experiments conducted with surface water, ground water, or deionized water as matrix may lead to different results. The application of deionized water in ozonation experiments has frequently been observed to lead to different reaction kinetics, TP distributions and even the formation of diverging TPs [98]. As shown in "Reactivity during oxidation" section, the mechanism of NDMA formation from tolylfluanid depends on the presence of catalytic amounts of bromide in the water matrix. In order not to skew the prioritization of toxicological relevant TPs, it is imperative to choose the experimental conditions as realistic as possible (i.e., close to actual conditions in waterworks). Overall, the selected experimental conditions have a great impact on the formation of TPs. We therefore propose the use of a surface or ground water for the experiments. Based on the indicator parameters listed in the EU Directive on the quality of water intended for human consumption, we propose that the used water matrix should have a pH value between 6.5 and 8 and a conductivity up to 2500 µS/cm at 20 °C [42]

The majority of micropollutants detected in the raw water resources typically occurs in the concentration range of ng/L to low µg/L [99]. Due to the oftentimes formation of multiple TPs, the concentration of TPs is always lower than the initial concentration of the applied test substance. In order not to miss relevant TPs due to lacking sensitivity we advise to split the experimental evaluation into two parts. In a first evaluation, experiments should be conducted with a relatively high initial concentration (e.g., upper µg/L) while keeping a realistic ratio of oxidant to applied test substance. The high initial test substance concentration facilitates the detection of TPs. The drawback of this approach is an improper interaction of the applied test substance and the water matrix as well as the interaction of oxidant and water matrix. To remedy this drawback, in a second experiment the concentration of applied test substance and oxidant is adjusted to realistic concentrations (e.g., higher ng/L to low µg/L range). The comparison of TPs formed in both experiments enables the prioritization of important TPs.

Experimental setup The experiments should be carried out using an appropriate experimental setup. The most common experimental setup is the use of batch experiments, in which the sample and oxidant are introduced into a reaction vessel under defined reaction conditions. After a defined reaction time an aliquot of the reaction mixture is withdrawn and quenched to prevent further

reaction. This experimental setup is easy to carry out and enables to precisely define reaction conditions such as reaction time, pH, temperature and oxidant concentration. However, studying a single treatment step is a major drawback because usually ozonation is combined with a biological post-treatment step [44]. Therefore, no conclusion about the fate of micropollutants in a combination of water treatment processes can be made.

A continuous lab-scale water treatment setup represents an alternative to batch experiments [100]. An example of a treatment scheme using ozonation, biofiltration and chlorination is shown in Fig. 10.

Contrary to a one-time dosing, sample and oxidant are continuously introduced and withdrawn. This continuous operation enables the combination of multiple treatment processes. A lab-scale ozonation combined with a post-treatment biological active sand filtration in a continuous experimental setup has already been established [101]. Due to the modular nature of the experimental setup, it is possible to investigate different water treatment schemes through rearranging the treatment modules. It is useful to collect samples after the biological treatment process for the investigation of the combined ozonation and biofiltration treatment. Similarly, it is advised to extend the reaction time of the chlorinated sample to simulate the additional time of the treated sample in the distribution network of a water supplier. We propose an additional reaction time of 1 day for chlorination.

Toxicity screening of reaction mixture obtained in the laboratory-scale simulation of water treatment

As a first screening option, we propose to conduct toxicity tests with the reaction mixture obtained from the lab-scale simulation of water treatment, before proceeding to the structure elucidation and quantification of individual TPs.

This effect-driven approach, aiming at prioritizing TPs, has already been proposed by other authors [6, 102]. In the effect-driven approach described by Escher and Fenner, toxicity testing is conducted on the reaction mixture. If the decrease in toxicity follows the decrease of parent compound concentration, the TPs are considered to be irrelevant. When toxicity increases or the decrease is not proportional to the parent compound concentration, further investigations are conducted to identify TPs.

Similarly to this proposal, effect-based trigger values have already been established for monitoring and assessing water quality [103]. This approach reduces the abundance of TPs and only TPs exceeding certain trigger value need to be further assessed.

In practice such an approach is already implemented in many water treatment plants which are using the UmuC test to evaluate gene mutation potential, according to DIN EN ISO 38415-T3 [104] for water treatment. The test system is already standardized and can therefore be easily implemented into a workflow. Gene mutation is likely the most sensitive endpoint and thus warrants the highest level of attention. This is also in line with the evaluation of genotoxicity in the workflow outlined above. In

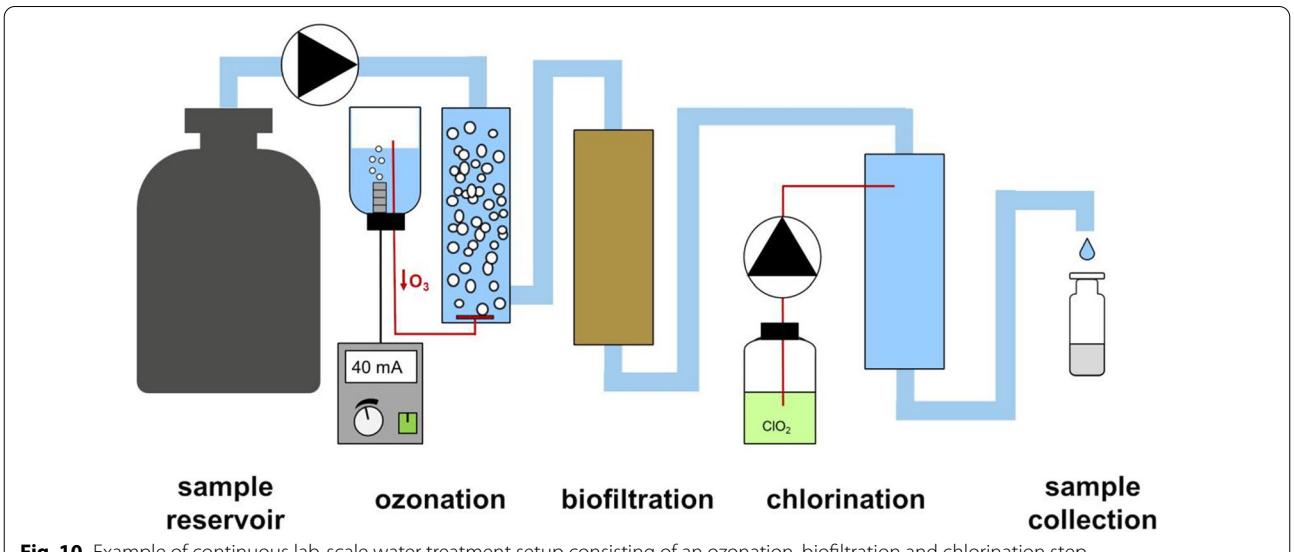


Fig. 10 Example of continuous lab-scale water treatment setup consisting of an ozonation, biofiltration and chlorination step

addition, the UmuC test is already available, easily implemented and validated.

For other toxicological endpoints, the test systems would need further development, standardization and ease of implementation. This is true for the in vitro micronucleus test (MNT), that uses mammalian cells and thus requires more sophisticated lab equipment and training as well as tests for endocrine activity. This is further complicated by the low concentration of individual TPs and the lack of suitable metabolizing systems for most in vitro assays.

The approach of testing treated water has the advantage that the actual exposure situation would be simulated. In addition, it could be included in monitoring programs. Control experiments on the toxicity of ozonated/chlorinated unspiked natural water should of course be included to determine if the effect originates from DBPs formed from natural substances present in the water or from TP(s) formed from the PPP residues.

If a positive result is obtained in the screening test, further work is required. This could for example be a fractionation of the reaction mix and testing of individual fractions/compounds to identify the transformation product driving the genotoxic event.

Step 5: Further experimental assessment—structure elucidation and quantification of individual major TPs

If the toxicity tests performed in step 4 on the reaction mixture obtained from the lab-scale simulation of water treatment indicate a concern, the origin of this enhanced toxicity should be investigated. This implies the identification and quantification of individual major TPs.

Detection of TPs

Liquid chromatography coupled with high-resolution mass spectrometry (LC–HRMS) using non-target screening (NTS) is a viable analytical method to detect TPs [80]. Briefly, samples are chromatographically separated and analyzed, and the MS data are searched for so-called features using a suitable peak finding algorithm. A feature is defined by its mass-to-charge ratio (m/z), retention time, and intensity [105]. By comparing the treated sample with a non-treated blank influent sample, a fold-change value can be derived [106]. TPs formed during the water treatment processes should have an enhanced intensity in the treated sample compared to the non-treated blank sample and therefore a significant fold-change value. We propose that TPs with a fold-change value of 5 are to be considered as potential TPs (e.g., fivefold increase of signal intensity due to the treatment process). A treated sample without the addition of the test substance can serve as a blank control to differentiate between TPs formed from test substance, and DBPs, formed from natural substances present in the water matrix. A Guideline for the use of non-target screening in water analysis has already been published [107].

Elucidation of the signals of interest is a multistep procedure, starting with the suggestion of empirical formulas according to the accurate mass of the HRMS measurement. The next level is the evaluation of MS/MS fragmentation spectra. Structures may be proposed based on interpretation of significant neutral losses. For an unambiguous assignment, the comparison of retention time and MS data with authentic reference material is necessary. In few cases, particularly concerning small molecules, potential TPs may be commercially available. Complex TPs, however, must typically be accessed via synthesis. Respective synthesis routes would need to be developed. As it is to be expected that not every TP can be assigned a structure proposal and suitable chemical synthesis will not be possible for all TPs, a clear guidance would be necessary how to proceed in such a case.

For unequivocal identification and quantification of the observed TPs, reference materials with known purity are essential. Alternatively, radio-labeled experiments could be envisaged. Radiolabeling of the test substance does not seem a realistic approach. Given the expected reactivity during oxidation, the complete assessment of TPs would require the labeling of virtually all atoms in the test substance.

Trigger value for major TPs

The abundance of formed TPs requires a prioritization step before structure elucidation and toxicological risk assessment is feasible. Only major TPs should have to be assessed further. Therefore, we propose the implementation of a TP relevance trigger value based on 10% signal intensity of the applied test substance (measured with LC–HRMS). A trigger value of 10% of initially applied substance is in line with the trigger set in the EU pesticide legislation [10] for the identification and inclusion of metabolites in the risk assessment and with the recommendations formulated in the OECD Guidelines for the testing of chemicals [108]. As an example, for an initial concentration of the applied test substance of 1 µg/L the trigger value of 10% leads to a threshold value of 100 ng/L for the transformation product (assuming ionization efficiency of applied test substance and transformation product is approximately equal). This threshold is comparable with the established trigger for pesticides and relevant metabolites in the EU [42] and offers enough safety while reducing the number of TPs, which need to be evaluated. In comparison, the health-related benchmark value [109] stipulates a first threshold for non-evaluated substances of 100 ng/L.

Step 6: Tiered dietary risk assessment of major TPs

If the concern of potentially harmful TPs has not been appropriately addressed in the previous steps, the risk of novel TPs to human health through the consumption of drinking water needs to be evaluated.

Only individual TPs significantly contributing to the dietary risk under realistic conditions should be included in a tiered dietary risk assessment. In these cases, the potential for exposure to the TP through the human diet and the compound-specific toxicity need to be evaluated. The type of studies or information required to ascertain the safety for consumers needs to be in alignment with the assessment/testing requirements for plant, livestock and processing residues in place in the EU and globally, as currently discussed on OECD level for the guidance document on the residue definition for risk assessment.

A TP could be considered "major" when present at a level $\geq 10\%$ of the initially applied test substance in experimental studies conducted under realistic conditions taking also post-treatments into account (step 5). This major TP would require structure elucidation, followed by an evaluation of the toxicological concern according to the decision scheme as aligned for plant, livestock and processing metabolites.

For water treatment, this approach is significantly more complex compared to plant, livestock and processing residues:

I. No EU standard water treatment regime is established.
II. The contribution of the actual PPP/metabolite and their interaction with the biological matrix or flocculation agents needs to be considered.
III. The synthesis of individual TPs is often very difficult, and in many cases, success may not be guaranteed with reasonable effort.
IV. The chemistry of the formed TPs will most likely not be covered by rat metabolism
V. It is difficult to get real exposure data—realistic concentrations of the TPs in drinking water as consumed.
VI. The contribution to the general exposure situation is difficult to evaluate since many pharmaceuticals, natural products and pesticides share common structural motifs, e.g., benzoic acid.

A clear, workable, European aligned guidance needs to be developed in order to provide both the applicant and the evaluator a path forward to avoid legal uncertainty and the potential for data gaps. This guidance would also need to define what the applicant has to demonstrate in case a compound cannot be synthesized, e.g., whether a surrogate compound may be tested.

In addition, a database of common TPs of natural compounds, chemicals, pesticides and pharmaceuticals, including exposure data, should be developed to allow for the assessment of the actual contribution of individual TPs to the overall exposure burden. As part of this, a risk cup approach could be developed to actually allow for the identification and potential reduction of the major contributors to the exposure. Such a database would also allow for an analysis whether *and* which mitigation methods would be considered adequate for a given chemistry.

In practice, the first endpoint to be investigated for a TP is genotoxicity, using the Ames test to assess mutagenicity and the in vitro micronucleus test to assess clastogenicity (including aneugenicity). Actual testing should not be performed for each individual compound, but rather guided by a combination of grouping based on chemical similarity, structural alerts, presence of organic functional groups and metabolic scaffolds followed by exposure assessment. Based on QSAR, read across and weight of evidence, group representatives are evaluated against thresholds of concern, (such as genotoxicity and other toxicological endpoints) and finally tested if insufficient data are available.

For TPs considered as major contributors, a tiered dietary consumer risk assessment should be performed. If a major TP is not deemed genotoxic, its general toxicity profile should be determined in line with the tox decision tree—first tier using the TTC—concept as tox reference values (Cramer Class III 1.5, Class II 9, Class I 30 µg/kg bw/day) [94] and the concentration found under realistic conditions in the experiment (Step 5) to avoid unnecessary toxicity testing and considering animal welfare. As drinking water consumption data volumes and body weights for different human consumers, e.g., WHO data [1] could be used with 100% allocation. If this indicative risk assessment would show any safety concerns for the consumer, Tier 2 will be tox testing of the TP according the EFSA and ECHA and internationally agreed guidance to derive reference values and refined risk assessment for the final evaluation of the risk for the consumer concerning the TP. For registered PPP a further Tier 3 for the risk assessment could be using EU monitoring data for the relevant TP in actual drinking water as consumed.

Conclusion

The present paper proposes a framework for the identification of potential concerns for public health resulting from TPs formed from PPP residues during drinking water treatment. The proposed tiered approach allows

the identification of concerns for public health, while avoiding unnecessary experimental testing, especially vertebrate testing.

Addressing the question of TPs formed during water treatment requires a multi-disciplinary approach, covering very diverse areas of expertise, from catchment modeling, in silico prediction tools and chemical structures database, to lab-scale simulation of water treatment, non-target analysis, toxicity testing, until dietary risk assessment. In each area, open questions remain, requiring further research and scientific discussions to reach consensus among the scientific and regulatory community.

Abbreviations

AOC: Assimilable organic carbon; BDOC: Biodegradable dissolved organic carbon; bw: Body weight; DBP: Disinfection by-products; DF: Dilution factor; DMS: *N,N*-Dimethylsulfamide; DOC: Dissolved organic carbon; ECHA: European Chemical Agency; EFSA: European Food Safety Authority; EU: European Union; GRDC: Global Runoff Data Centre; HAA: Haloacetic acid; HPLC: High-performance liquid chromatography; HRMS: High-resolution mass spectrometry; LC–HRMS: Liquid chromatography–high-resolution mass spectrometry; MNT: Micronucleus test; MS: Mass spectrometry; NDMA: *N*-Nitrosodimethylamine; NOM: Natural organic matter; NTS: Non-target screening; OECD: Organisation for Economic Cooperation And Development; PEC: Predicted environmental concentration; PPP: Plant protection product; QSAR: Quantitative structure–activity relationship; SWAT: Soil and water assessment tool; THM: Trihalomethane; TP: Transformation product; TTC: Threshold of toxicological concern; UDMH: Unsymmetrical dimethylhydrazine.

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Author contributions

Each author made substantial contributions to the drafting of the manuscript. The writing of each section was distributed based on the authors' area of expertise: "Step 1: Exposure assessment" section was written by SL, TS and SG. "Step 2: Reactivity assessment (oxidation and other treatment steps)" section was written by AM, DA and ND and reviewed by RD. "Step 3: Toxicity screening based on TTC concept" section was written by MFrericks. "Step 4: Experimental assessment—laboratory-scale simulation of water treatment and toxicity testing of reaction mixture" section was written by MFlörs and WS ("Laboratory-scale simulation of water treatment" section) and by MFrericks ("Toxicity screening of reaction mixture obtained in the laboratory-scale simulation of water treatment" section). "Step 5: Further experimental assessment—structure elucidation and quantification of individual major TPs" section was written by MFlörs, WS and ND. Writing of "Trigger value for major TPs" section and the definition of the trigger was a collegial effort with contribution of all authors. "Step 6: Tiered dietary risk assessment of major TPs" section was written by AB-B and MFrericks. AM led revisions of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

AM, AB-B, ND, RD, MFrericks, SL, SG, TS are employed by a chemical manufacturing company.

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