Chemosphere 325 (2023) 138259

Contents lists available at ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

# An integrated human health risk assessment framework for alkylphenols due to drinking water and crops' food consumption

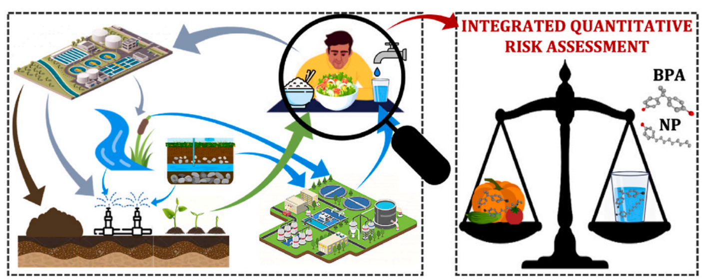
Luca Penserini, Beatrice Cantoni, Marco Gabrielli, Elena Sezenna, Sabrina Saponaro, Manuela Antonelli *

*Politecnico Milano, Department of Civil and Environmental Engineering (DICA), Environmental Section, Piazza Leonardo da Vinci 32, 20133, Milano, Italy*

## HIGHLIGHTS

- An integrated risk assessment for multiple exposures to contaminants was created.
- Contaminants exposure comparison between drinking water and crop food was performed.
- Health risk due to NP is not negligible, but BPA risk is significantly higher.
- Crops' food intake is the main alkylphenols exposure source compared to tap water.
- Analytical and data gaps exist on CECs monitoring in interconnected compartments.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

Handling editor: Renato Somma

*Keywords:*
Contaminants of emerging concern
Human health risk assessment
Drinking water quality
Food consumption
Water consumption
Human dietary exposure
ONE Health
Bisphenol a
Nonylphenol
Limit of quantification

## ABSTRACT

The increasing overexploitation and pollution of freshater resources are potential threats for public health, causing cross-contamination among the interconnected environmental compartments (freshwater, soil, crops). In particular, contaminants of emerging concern (CECs) originating from anthropic activities are not completely removed by wastewater treatments plants. This leads to their presence in drinking water (DW) sources, soil and crops intended for human consumption due to discharges of treated wastewater in surface waters and direct wastewater reuse practices. Currently, health risk assessments are limited to single exposure sources without considering the multiple exposure routes to which humans are subjected. For instance, among CECs, bisphenol A (BPA) and nonylphenol (NP), respectively, adversely affect immune and renal systems and have been frequently detected in DW and food, their major exposure sources for humans. Here, an integrated procedure is proposed to quantitatively assess health risk from CECs due to multiple exposure from the consumption of both DW and food, considering the relevant inter-connected environmental compartments. This procedure was applied to BPA and NP to calculate their probabilistic Benchmark Quotient (BQ), showing its potential in quantitatively apportioning the risk between contaminants and exposure sources, and its use as a decision support tool for prioritizing mitigation measures. Our results indicate that, even though the human health risk due to NP is not negligible, the estimated risk due to BPA is significantly higher, and the consumption of food from edible crops determines a higher risk compared to tap water. Hence, BPA is undoubtedly a contaminant to be prioritized, especially through mitigation actions aimed at its prevention and removal from food.

* Corresponding author.
*E-mail address:* manuela.antonelli@polimi.it (M. Antonelli).

https://doi.org/10.1016/j.chemosphere.2023.138259
Received 30 September 2022; Received in revised form 31 January 2023; Accepted 26 February 2023
Available online 3 March 2023

**List of abbreviations**

| | |
|---|---|
| BPA | Bisphenol A |
| BQ | Benchmark Quotient |
| $C_{EXP}$ | Exposure Concentration |
| CECs | Contaminants of Emergin Concern |
| CER | Cereals |
| CSO | Combined Sewer Overflow |
| $Dose_{EXP}$ | Exposure Dose |
| DW | Drinking Water |
| DWTP | Drinking Water Treatment Plant |
| EFSA | European Food Safety Authority |
| FV | Fruits and Vegetables |
| GW | Groundwater |
| HBGV | Health-Based Guidance Value |
| IR | Intake Rate |
| LOQ | Limit Of Quantification |
| $LOQ_{LIM}$ | Maximum risk-based LOQ |
| $MLE_{LC}$ | Maximum Likelihood Estimation method for Left-Censored data |
| NP | Nonylphenol |
| P | Allocation factor |
| P(BQ > 1) | Probability of BQ higher than 1.0 |
| P(BQ > 0.1) | Probability of BQ higher than 0.1 |
| PET | Polyethylene |
| QCRA | Quantitative Chemical Risk Assessment |
| RfD | Reference Dose |
| SW | Surface Water |
| TAP | Tap Water |
| TDW | Treated Drinking Water |
| TWW | Treated Wastewater |
| UWW | Untreated Wastewater |
| WW | Wastewater |
| WWTP | Wastewater Treatment Plant |

## 1. Introduction

The unprecedented scarcity of clean freshwater that many world regions are experiencing due to growing population, increasing urbanization and food demand, is enhanced by climate change and is becoming a major issue for present and future generations (Kummu et al., 2016). Besides quantity issues, also there's growing concern regarding water quality. Indeed, the increasing level of water pollution in groundwater (GW) and surface water (SW) and the potential cross-contamination among environmental compartments (water, soil, crops) amplify human health risk (IPCC, 2022). In particular, great attention should be paid to contaminants of emerging concern (CECs), which have already been detected worldwide in SW, GW, and soils (Rashtian et al., 2019).

In fact, CECs of anthropic origin, which are not completely removed by wastewater treatment plants (WWTPs), can end up in the recipient SW or GW, both used as drinking water (DW) sources, potentially persisting and exceeding acceptable levels (Gogoi et al., 2018). Furthermore, when freshwater water and reclaimed wastewater (WW) are directly or indirectly used for irrigation, CECs can be directly uptaken in crops intended for human consumption or accumulate in soil and translocate into crops over time (Careghini et al., 2015).

Among CECs, alkylphenols, specifically bisphenol A (BPA) and nonylphenol (NP), critical for immune and renal systems, respectively, are frequently detected in several environmental compartments (de Bruin et al., 2019; Torres-García et al., 2022). Regarding these two compounds, additional contaminations of DW and food from edible crops (hereinafter referred to as food) may derive from materials in contact with them, as (i) lining resins in the DW distribution network from DW treatment plants (DWTPs) to taps (Cantoni et al., 2021a), (ii) plastic bottles in bottled water (Hahladakis et al., 2022), and (iii) food packaging (Muncke, 2021). Hence, considering the multiple exposure routes for humans and the related adverse effects of BPA and NP, the contributions of DW and food should be considered in an integrated framework, rather than focusing only on stand-alone compartments.

The implementation of risk-based approaches aimed at the preventive control of health risk is strongly suggested by recent regulations (European Commission, 2020; WHO, 2017). However, although CECs are frequently detected in many environmental compartments, only few studies attempted to evaluate the occurrence and the human health risk related to CECs starting from the different sources, analyzing their fate through the various interconnected water (SW, GW, DW and WW) and solid (biosolids, soil and food) matrices. Typically, this is done in critical reviews aiming at quantifying CEC concentrations in different compartments, as Careghini et al. (2015) and Torres-García et al. (2022), which highlighted that these contaminants occur with high variability and with a relevant percentage of censored data, namely data lower than the analytical limit of quantification (LOQ). Other studies assessed the health risk limited to a single source of exposure related to a specific compartment. For example, Penserini et al. (2022) applied the Quantitative Chemical Risk Assessment (QCRA) procedure developed by Cantoni et al. (2021b) to quantitatively estimate the risk generated by alkylphenols exposure due to only DW consumption (both for tap and bottled water), while Delli Compagni et al. (2020) and Revitt et al. (2021) focused risk assessment from CECs on the consumption of food from crops irrigated with reclaimed WW. However, to the best of the authors' knowledge, there are no research studies evaluating and comprehensively comparing multiple exposures to CECs estimating the relative impact of each exposure source. Moreover, a fully stochastic approach for the risk assessment would be highly beneficial, since it would enable to consider the uncertainties that are inevitably associated to both the measurement of CEC concentrations and their toxicological characterization (Cantoni et al., 2021b).

The present work proposes an integrated procedure to quantitatively assess the chemical risk due to CECs from the consumption of both DW and food, considering multiple exposure deriving from the interconnected environmental compartments involved in DW and food production as described above. The procedure accounts for the uncertainties related to the variability of contaminant concentration values and percentage of censored data. Among CECs, BPA and NP were considered as reference CECs as they are in the list of compounds included in the revision of the European Drinking Water Directive (European Commission, 2018) and in the watch list of substances of concern for water intended for human consumption (European Commission, 2022), respectively. For these two compounds, a high number of concentration data in the different environmental compartments are available, providing robustness to the described procedure and results.

## 2. Materials and methods

### 2.1. System boundaries definition and data collection

The relevant and interconnected environmental compartments regulating the fate of BPA and NP from sources to consumers were identified, namely: GW, SW, treated drinking water (TDW), consumed tap water, consumed bottled water, untreated wastewater (UWW), treated wastewater (TWW), biosolids, agricultural soil and food, either as cereals or as fruit and vegetables. In Fig. 1a, the conceptual scheme of the studied system is shown, highlighting the variety of connections among the different environmental compartments.

For BPA and NP, maximum concentration data and LOQ values associated with the corresponding analytical methods were collected from literature studies referred to environmental compartments above listed, regardless of their geographical origin. Only studies reporting results collected under representative conditions (i.e., field monitoring, realistic case studies) were considered. For GW, SW and agricultural soils, data reported in studies addressing sites located in proximity of industrial effluents or significant sources of contamination were not considered. For UWW, TWW and biosolids, only data related to urban WWTPs were considered. For bottled water, only data related to PET (polyethylene) bottles, analyzed right after their purchase (i.e., without home storage effects) were used. Finally, for cereals, fruit and

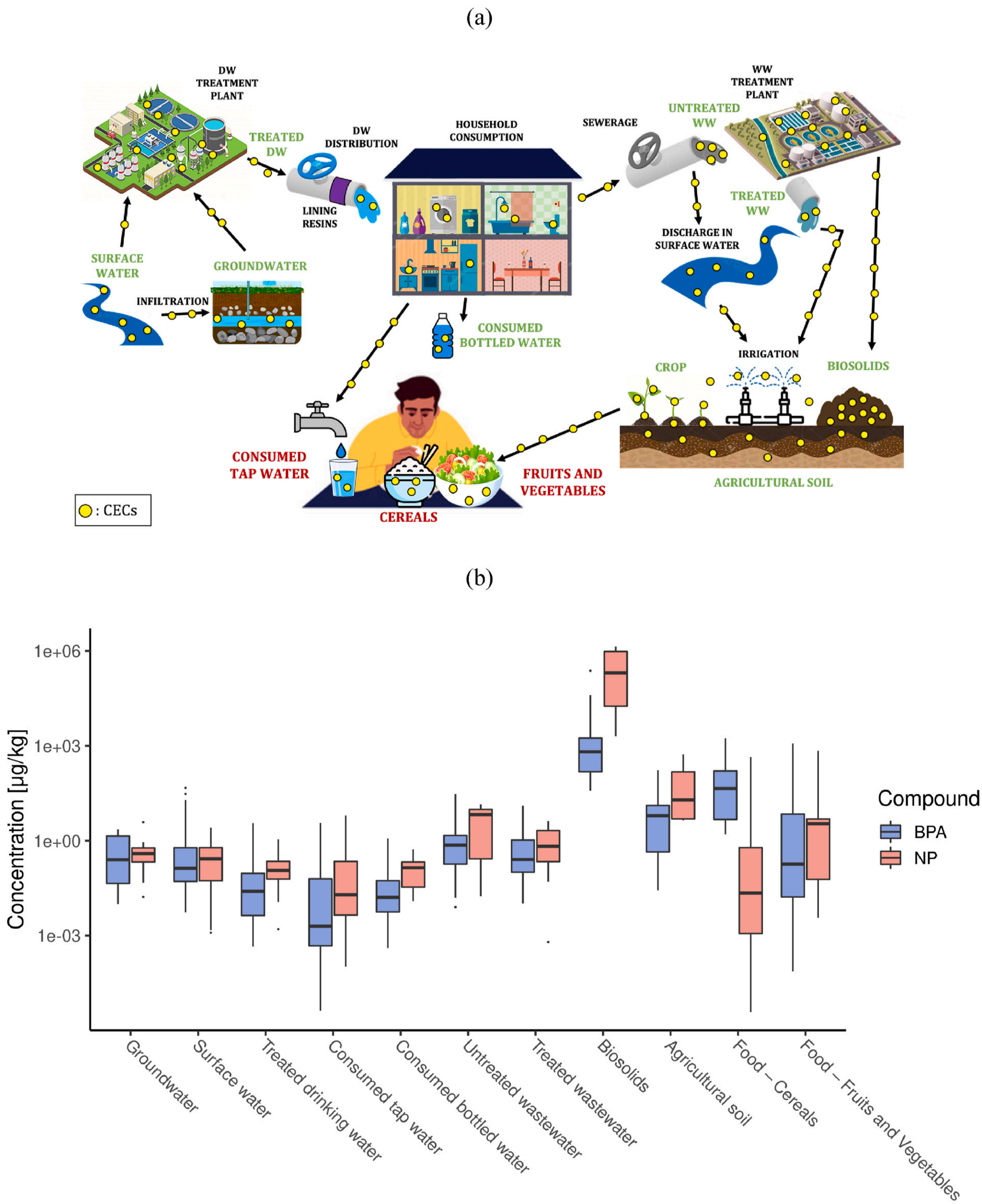



**Fig. 1.** A) Conceptual scheme of the studied system, indicating all the considered environmental compartments (in green), including the studied exposure sources (in red), together with their connections (in black). b) Boxplots of concentrations of BPA and NP in the different compartments. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

vegetables, only concentrations measured in unpacked raw products, directly collected from crops or local markets, were considered.

For each environmental compartment, the number of available studies and data, the statistical summary data and the percentage of data below the LOQ are reported in Table 1, while more detailed information about the studies are reported in Table S1. A total of 184 papers have been consulted, and 144 have been used for the work presented here, resulting, in 507 and 307 concentration values for BPA and NP, respectively (Table 1, column "# available data").

### 2.2. Quantitative Chemical Risk Assessment modelling

The model for the QCRA proposed by Penserini et al. (2022) was applied to evaluate multiple exposure to the two contaminants from the consumption of both DW and food.

The investigated exposure route was oral ingestion, thus, only tap water and food, specifically cereals, fruit and vegetables, were considered as the exposure sources for risk assessment. Consumed bottled water was excluded from risk assessment to be aligned to food evaluations, for which only products that have not been in contact with packaging materials were considered. Actually, BPA and NP migration within the consumed products due to the release from packaging materials was beyond the scope of this study. The choice of excluding from the analysis the contribution of water and food packaging is due to limitations in the currently available data about CECs migration from packaging materials to food and water. Firstly, the number of data is low and the diverse experimental conditions (e.g. packaging material, contact surface area, food nature, processing procedures, storage temperature and duration, packaging overuse or recycling, etc.) are hard to be compared, making it difficult to generalize any migration pattern to be used in risk assessment. In addition, it is impossible to address independently and in a robust way the contributions of both the environmental sources and packaging, since most of the studies addressing CECs presence in food aims at evaluating the general dietary exposure, neglecting the food life history.

The QCRA was articulated in three steps: (i) in the exposure assessment, the contaminant's dose ($Dose_{EXP}$) to which the consumer is exposed was determined starting from exposure concentrations ($C_{EXP}$) and actual intake rates (IR) of DW and food; (ii) in the hazard assessment, dose-response data from toxicological studies are used to estimate the Health-Based Guidance Value (HBGV), and (iii) in risk characterization, results from previous steps were combined to estimate the Benchmark Quotient (BQ) distributions, including uncertainty analysis.

#### 2.2.1. Exposure assessment

Data collected from literature were used to estimate, for both contaminants, the statistical distributions of concentrations in tap water ($C_{EXP,TAP}$), cereals ($C_{EXP,CER}$), and fruit and vegetables ($C_{EXP,FV}$), according to the procedure explained in detail in section S1.1. Since a notable set of concentration data was lower than the LOQ (Table 1), the Maximum Likelihood Estimation method for left-censored data ($MLE_{LC}$), explained in Cantoni et al. (2020), was applied to fit statistical distributions to include censored data in the $C_{EXP}$ estimation and not losing the information hidden in them. Then, 1000 values were sampled independently from each $C_{EXP}$ statistical distribution (6 in total: 3 exposure sources for 2 contaminants). To account for censored data, boxplots of the investigated contaminant concentrations in the different matrices were plotted through the *cenboxplot* function from the NADA v1.6–1.1 package (Helsel, 2012) in R v4.1 (R Core Team, 2022).

For tap water, the statistical distribution for daily water consumption obtained by Penserini et al. (2022), based on real water consumption data from studies worldwide, were used. For cereals and fruit and vegetables, the European Food Safety Authority (EFSA) Comprehensive European Food Consumption Database (EFSA, 2011) was used to collect real food consumption data, from which the related statistical distributions were obtained as explained in section S1.1. Only data related to unprocessed cereals, fruit and vegetables were considered. For both water and food consumption, only data referred to adults were accounted for. Then, daily water and food consumptions were converted into IR (L $kg^{-1}$ $day^{-1}$ for water, g $kg^{-1}$ $day^{-1}$ for food) by dividing them by the average body weight, assumed constant and equal to 60 kg for adults (WHO, 2017).

**Table 1**
Summary of the $C_{EXP}$ collected from literature for BPA and NP for each compartment, reporting: number of available studies and data, concentration range, mean, standard deviation, and percentage of data below the LOQ.

| Compartment | Contaminant | # available data | # available studies | Range | Mean | Standard deviation | Data below LOQ [%] | Unit |
|---|---|---|---|---|---|---|---|---|
| Groundwater | BPA | 10 | 9 | 0.01–2.30 | 1.04 | 1.17 | 0.00 | μg $L^{-1}$ |
| | NP | 8 | 8 | 0.02–3.85 | 0.81 | 1.26 | 0.00 | μg $L^{-1}$ |
| Surface water | BPA | 95 | 55 | 0.0055–46.70 | 2.27 | 7.42 | 4.21 | μg $L^{-1}$ |
| | NP | 37 | 13 | 0.0012–2.55 | 0.54 | 0.62 | 8.11 | μg $L^{-1}$ |
| Treated drinking water | BPA | 37 | 12 | 0.0005–3.57 | 0.19 | 0.67 | 24.32 | μg $L^{-1}$ |
| | NP | 34 | 11 | <0.0001–1.10 | 0.20 | 0.22 | 32.35 | μg $L^{-1}$ |
| Consumed tap water | BPA | 88 | 27 | <0.0001–3.61 | 0.20 | 0.59 | 40.91 | μg $L^{-1}$ |
| | NP | 95 | 17 | <0.0001–6.19 | 0.53 | 1.04 | 40.00 | μg $L^{-1}$ |
| Consumed bottled water | BPA | 54 | 13 | <0.00001–1.18 | 0.10 | 0.21 | 22.22 | μg $L^{-1}$ |
| | NP | 42 | 11 | <0.006–0.54 | 0.18 | 0.13 | 19.05 | μg $L^{-1}$ |
| Untreated wastewater | BPA | 32 | 14 | <0.005–29.74 | 2.79 | 5.85 | 12.50 | μg $L^{-1}$ |
| | NP | 7 | 5 | 0.0176–14.18 | 5.95 | 5.74 | 0.00 | μg $L^{-1}$ |
| Treated wastewater | BPA | 31 | 14 | 0.0104–9.40 | 0.93 | 1.81 | 0.00 | μg $L^{-1}$ |
| | NP | 10 | 7 | 0.0006–4.20 | 1.29 | 1.45 | 0.00 | μg $L^{-1}$ |
| Biosolids | BPA | 21 | 7 | 63.60–236,000 | 14,925 | 52,769 | 4.76 | μg $kg^{-1}$ |
| | NP | 6 | 3 | 2000–1,359,000 | 547,533 | 599,225 | 0.00 | μg $kg^{-1}$ |
| Agricultural soil | BPA | 55 | 16 | <0.0042–167.90 | 21.48 | 43.74 | 7.27 | μg $kg^{-1}$ |
| | NP | 8 | 5 | 4.43–542.00 | 127.78 | 195.84 | 0.00 | μg $kg^{-1}$ |
| Food - Cereals | BPA | 22 | 5 | 1.60–1740 | 176.11 | 376.83 | 0.00 | μg $kg^{-1}$ |
| | NP | 18 | 2 | <0.06–440 | 86.50 | 165.37 | 55.56 | μg $kg^{-1}$ |
| Food – Fruits and vegetables | BPA | 62 | 11 | <0.0009–1188 | 48.53 | 183.43 | 27.42 | μg $kg^{-1}$ |
| | NP | 42 | 5 | <0.0007–700.00 | 23.90 | 119.49 | 23.53 | μg $kg^{-1}$ |

Once the 1000 $C_{EXP}$ values were sampled for each exposure source and contaminant, they were multiplied by the 1000 values of IR sampled from the statistical distribution of the corresponding source, to derive 1000 values of $Dose_{EXP}$ [μg kg$^{-1}$day$^{-1}$], as:

$$Dose_{EXP,i,j} = C_{EXP,i,j} \times IR_j \tag{1}$$

where *i* is the contaminant and *j* the exposure source.

#### 2.2.2. Hazard assessment

The contaminant adverse effect doses on the critical endpoint were determined by defining a HBGV, which is the contaminant dose that does not result in the exceedance of the tolerable exposure over the consumer lifetime (WHO, 2006). HBGV [μg kg$^{-1}$ day$^{-1}$] was calculated as (Baken et al., 2018):

$$HBGV = RfD \times P \tag{2}$$

where RfD [μg kg$^{-1}$ day$^{-1}$] is the reference dose and P [%] is the allocation factor that is the percentage of risk maximally associated to oral ingestion compared to the overall exposure routes, considered as constant and equal to 20% (Baken et al., 2018).

For the RfD estimation, toxicological data were collected from the latest toxicological scientific opinions available. For BPA, a draft scientific opinion published by the EFSA (2021) was used where BPA's critical endpoint was re-evaluated. Conversely from EFSA (2015), the decreased kidney weight was identified as the critical endpoint for BPA, with a RfD equal to 4 μg kg$^{-1}$ day$^{-1}$, EFSA (2021) reported a RfD of 0.04 ng kg$^{-1}$ day$^{-1}$, determined by identifying the immune system as the critical endpoint (Luo et al., 2016). For NP, kidney (decrease in weight) was still identified as the critical endpoint, thus the RfD equal to 1.33 μg kg$^{-1}$ day$^{-1}$ was applied (Penserini et al., 2022).

#### 2.2.3. Risk characterization

BQ values were computed for each contaminant *i* and each exposure source *j* as:

$$BQ_{i,j} = \frac{Dose_{EXP,i,j}}{HBGV_i} \tag{3}$$

A Monte Carlo simulation method was applied, which allowed for the propagation of the uncertainties related to the estimated distributions of $C_{EXP}$ and IR (resulting in the 1000 $Dose_{EXP}$ data points) into 1000 BQ values (Cantoni et al., 2021b), for the 6 combinations of contaminants and exposure routes (section S1.1). The obtained values were used to estimate the BQ statistical distributions, then employed to extrapolate the probability of BQ higher than a threshold value, namely BQ equal or larger than: (i) 1 ($P(BQ > 1)$), and (ii) 0.1 ($P(BQ > 0.1)$). $P(BQ > 1)$ and $P(BQ > 0.1)$ express the percentage of the total area underlying the BQ probability density curve that is above the BQ value of 1.0 and 0.1, respectively.

### 2.3. Determination of the maximum risk-based LOQs

According to all the steps included in the QCRA procedure, the maximum risk-based LOQs were calculated. Risk-based LOQ represents the LOQ that the analytical methods applied for BPA and NP monitoring should not exceed to guarantee the measurement of concentrations low enough to comply with the HBGVs. Hence, the maximum risk-based LOQ ($LOQ_{LIM}$) was defined as the minimum requirement to estimate the risk, meaning a BQ equal to 1, targeted as the limit value to identify a potential concern for human health (Baken et al., 2018). It was derived from Eqs. (2) and (3) as:

$$LOQ_{LIM,i,j} = \frac{HBGV_i}{IR_j} \tag{4}$$

For each exposure route and contaminant, two different values of $LOQ_{LIM,i,j}$ were calculated: (i) a constant value, assuming a constant $IR_j$, and (ii) the distribution based on the distribution of actual IRs (paragraph 2.2.2.2). For DW, the constant IRj value was 0.033 L kg$^{-1}$ day$^{-1}$, corresponding to the default precautionary value used in risk assessment (obtained by dividing 2 L inhab$^{-1}$ day$^{-1}$ by the body weight, 60 kg inhab$^{-1}$) (WHO, 2017), while the distribution of actual IRs was taken from Penserini et al. (2022). For cereals and fruit and vegetables, the constant $IR_j$ were obtained as the average values of the consumption data collected from EFSA (2011), respectively 0.549 g kg$^{-1}$ day$^{-1}$ and 0.852 g kg$^{-1}$ day$^{-1}$, while the same groups of data from the same datasets were used for the estimation of the realistic consumption $IR_j$ distributions.

## 3. Results and discussion

### 3.1. Compartments' concentrations

The conceptual scheme in Fig. 1a supports the comprehension of the chart in Fig. 1b, where the boxplots of the concentration data collected from literature are reported, for each environmental compartment and contaminant. It must be reminded that concentrations are not directly correlated from one compartment to another, since they come from independent studies considering different geographical regions and, in most cases, one single compartment at a time. The mean value and the range values of the collected compartment-specific concentrations of BPA and NP are reported in Table 1.

As for BPA (507 values from 127 articles) and NP (307 values from 59 articles), a high variability characterizes most of the compartments, with concentrations ranging from $10^{-5}$ to $10^{1}$ $\mu g_{BPA}$ L$^{-1}$ in water matrices and $10^{-4}$ to $10^{5}$ $\mu g_{BPA}$ kg$^{-1}$ in solid matrices, and from $10^{-4}$ to $10^{1}$ $\mu g_{NP}$ L$^{-1}$ in water matrices and $10^{-4}$ to $10^{6}$ $\mu g_{NP}$ kg$^{-1}$ in solid matrices. This marked variability is also found inside the single compartment, where the concentration ranges are notably different from one to the other; for instance, in GW, a difference of 2 orders of magnitude in the range of both contaminants is found, while the difference is of 7 and 6 orders of magnitude respectively for BPA and NP in fruits and vegetables. The higher variability lies in the solid matrices, which are also the compartments with a lower number of available articles (Table 1).

Even though a significant comparison among the concentration values from different compartments is confounded by the concentration variability in each compartment, the data suggests that BPA and NP concentrations decrease after water treatments, i.e. from GW and SW to the three categories of DW, and from UWW to TWW, while they slightly rise from consumed DW to UWW. On the other side, biosolids is the compartment with the highest concentrations, especially for NP, while the two contaminants show different behavior in the other solid matrices: cereals display higher BPA concentration compared to both soil and fruits and vegetables, while NP concentrations are the lowest in cereals. Besides specific conditions of the studies reported in literature, this difference might be due to (i) the type of irrigation used to water the different crops (Lu et al., 2015), (ii) the variability in the physiological characteristics in plant species (Christou et al., 2019), and (iii) the different chemical-physical properties of the two contaminants, i.e. lipophilicity and biodegradability, which affect the fate in soil and the uptake and translocation of contaminants into plants (Bagheri et al., 2021).

### 3.2. Comparison between the reported LOQs and the risk-based LOQs

Since consumed tap water and food are the most sensitive compartments for human health risk assessment, it is crucial to accurately measure BPA and NP concentrations in these compartments, independently from the risk assessment framework used. Table 1 shows that BPA and NP monitoring studies are characterized by high percentages of censored data, especially for consumed tap water and food. However, concentration data below LOQ do not necessarily imply the lack of risk for human health. In fact, to properly evaluate whether the exposure to a certain contaminant poses a risk for human health, the analytical methods applied to measure the exposure concentrations should be characterized by a LOQ low enough to ensure at least the quantification of the HBGV, and so to ensure at least a BQ equal to 1.

The $LOQ_{LIM}$ estimated through Eq. (4) for each contaminant and exposure route is shown in Fig. 2 both as a constant value, assuming a constant IR for water and food consumption, and as a distribution, considering the actual consumption rates as IR distributions (Paragraph 2.2.1). For BPA, the constant $LOQ_{LIM}$ for tap water, cereals, and fruits and vegetables are $2.4 \times 10^{-4}$ μg $L^{-1}$, $1.5 \times 10^{-2}$ μg $kg^{-1}$ and $1 \times 10^{-2}$ μg $kg^{-1}$, respectively, while for NP, they are 4 μg $L^{-1}$, 240 μg $kg^{-1}$ and 155 μg $kg^{-1}$, respectively.

In Fig. 2, the LOQ values reported in the 65 studies monitoring BPA and NP in tap water, cereals, fruits and vegetables are compared to the $LOQ_{LIM}$ to evaluate whether the analytical methods applied in the available literature are capable to properly evaluate the presence of human health risk.

Firstly, the LOQ values found in the literature for both BPA and NP cover a wide range of values. Tap water is the exposure route with the wider range of LOQs ($10^{-5}$– 8 μg $L^{-1}$ for BPA and $10^{-5}$–0.2 μg $L^{-1}$ for NP), while LOQ values for cereals have the smallest range ($10^{-2}$– 0.5 μg $kg^{-1}$ for BPA and $10^{-2}$ -0.2 μg $kg^{-1}$ for NP). Such LOQ values are low enough for NP in all the exposure routes to discriminate whether the exposure concentration is below or above the HBGV. As for BPA, several studies adopted analytical methods with a LOQ higher than the $LOQ_{LIM}$. Specifically, the percentage of BPA studies in which the $LOQ_{LIM}$ is exceeded for water, cereals, fruits and vegetables are 82.8%, 100% and 91.7%, respectively. Such high percentages of studies not complying with the $LOQ_{LIM}$ values for BPA are due to the RfD identified by EFSA (2021) for BPA effects on the immune system, which is 5 orders of magnitude lower compared to the previous RfD of 2015 for kidney as the endpoint. Clearly, this RfD reduction needs to be followed by analytical methods for BPA measurements in both tap water and food to lower the LOQs.

### 3.3. Human health risk apportionment between drinking water and food

Although BPA concentrations are often measured as lower than LOQs, the adopted analytical methods do not guarantee that the censored concentrations are lower than the required values for compliance with the HBGV, increasing the uncertainties in the risk estimation. Therefore, not to lose significant information about the actual concentrations of the contaminants in the various environmental compartments, left-censored data should be included into the fitted $C_{EXP}$ statistical distributions. Feeding these distributions as inputs to the QCRA procedure for the probabilistic quantification of the human health risk, it is possible to account for the high variability associated to $C_{EXP}$, properly considered within the uncertainty analysis.

The results of the risk characterization are reported in Fig. 3a, where the obtained BQ distributions for each analyzed exposure source and contaminant are reported as violin plots, together with four horizontal lines corresponding to BQ threshold values equal to 0.1, 0.2, 0.6 and 1: the first three values can be used as quantitative early-warning health risk values, while the threshold equal to 1 identifies the presence of a risk (Baken et al., 2018).

Considering the BQ values for BPA, the BQ distribution of all sources are located almost completely above the threshold of 1, with a $P(BQ > 1)$ of 65%, 99.9% and 74.6% respectively for tap water, cereals and fruits and vegetables. This clearly indicates the presence of a potential human health concern from BPA due to the consumption over a lifetime period of either DW or food. An opposite situation is determined for NP, where $P(BQ > 1)$ are equal to 0.6%, 0.4% and 1.0% for tap water, cereals, and fruits and vegetables, showing a significant lower likelihood for human health risk compared to BPA. However, being the main fraction of the BQ estimated distributions for NP located below 1, it is worth evaluating the estimated $P(BQ > 0.1)$, which indicates the probability for the consumer to ingest products which need further investigation to understand if a toxic effect could be displayed (Schriks et al., 2010). The estimated $P(BQ > 0.1)$ values for NP are equal to 5.6% for tap water, 4.3% for cereals and 8.0% for fruits and vegetables, pointing out a not negligible probability for a potential human health concern, suggesting thus the need for further investigations (i.e. monitoring campaigns,

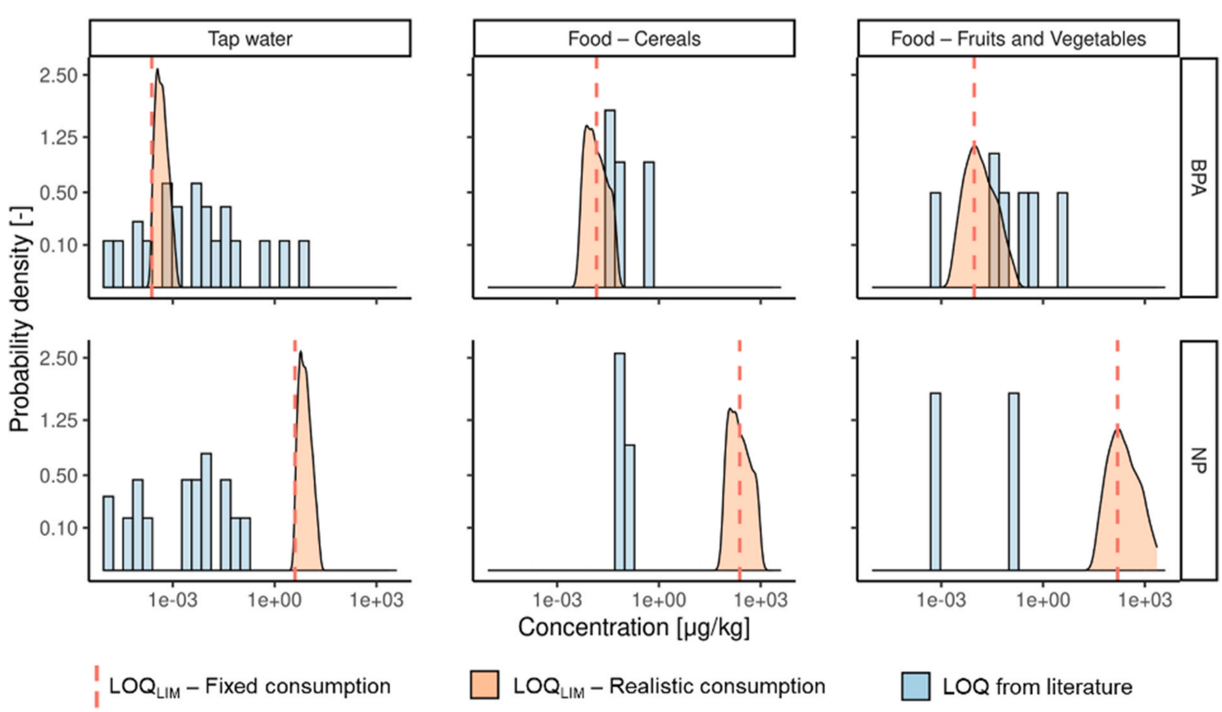



**Fig. 2.** Comparison of the LOQs reported in literature with the maximum risk-based $LOQ_{LIM}$, in case of constant IR or a distribution, for each contaminant and exposure source.

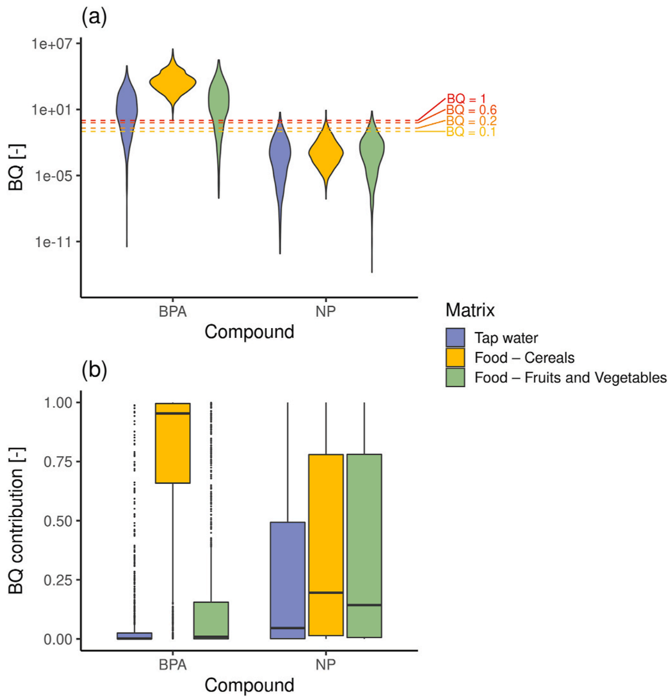



**Fig. 3.** Estimated (a) BQ distributions for each risk source, with the (b) related contribution to the overall risk. Dashed lines indicate BQ values equal to the thresholds of 0.1, 0.2, 0.6, 1.

toxicological studies or specific risk assessment).

Exposure routes responsible for the highest contribution to the overall risk require interventions' prioritization aimed at risk reduction. To identify the relative importance of each exposure route, their contribution to the overall risk was estimated as a percentage distribution to determine the risk apportionment (Fig. 3b). For BPA, cereals' contribution is much higher than the other sources, followed by fruits and vegetables and tap water, with average contributions equal to 77.6%, 15.8% and 6.6%, respectively. For NP the situation is quite balanced, with risk from food consumption (37.6% for cereals and 35.5% for fruits and vegetables), slightly higher than for tap water (26.9%). This reflects the values of concentrations of the sources (Fig. 1b), where BPA is significantly more present in cereals rather than in fruits and vegetables, while NP is equally spread.

It can be concluded that both tap water and food consumption exposure routes are critical for human health risk due to these two contaminants. Although the risk due to NP is not negligible, the human health concern due to BPA is significantly higher. On the other side, cereals and fruits and vegetables consumption determines a higher risk compared to tap water. Therefore, in a perspective of identifying the most effective interventions for risk reduction, BPA is undoubtedly a contaminant to be prioritized, especially through measures addressing its prevention and removal from food.

### *3.4. Considerations on risk reduction interventions and further sources of risk*

As human health risk from anthropogenic contaminants derives from multiple sources, risk assessments need to embrace the complexity of the possible exposure routes, sketched in Fig. 1a, and priority mitigation actions should be ranked based on their contribution in risk reduction. Given the risk contributions highlighted for BPA and NP in Fig. 3, interventions on tap water would only provide a limited effect on the overall risk reduction. On the contrary, interventions on food would prove as more effective, as both cereals and fruits and vegetables shown the highest risk contributions, especially for BPA. Choosing the alternatives that maximize the overall expected risk reduction could be a criterion to rank interventions. In light of this, interventions should be preferred either if they provide high efficiency on a single compartment, for example dedicated treatment steps during DW treatment, e.g. adsorption on activated carbon (Westerhoff et al., 2005), or if they follow a more preventive approach that affects multiple compartments, even though providing lower single reduction efficiencies. Examples of this latter approach consist in strategies targeted at curbing entrance of potentially harmful contaminants in the environment, such as imposing bans on harmful contaminants or certain products (European Commission, 2016), or enhancing wastewater and sludge treatment (Guerra et al., 2015).

To evaluate the effectiveness and the feasibility of different interventions applied to the compartments included in Fig. 1a to reduce the overall health risk, it is necessary to: (i) conceptualize the cause-effect links among the different compartments, and (ii) collect data on fate of BPA and NP in the different compartments up to the exposure sources. This was performed through the scheme in Fig. 4, where all the compartments and the two exposure sources (DW and food) are reported as squared nodes, while the cause-effect links among them are reported with arrows labeled with the nature of the link affecting CEC's fate. To draw the figure, the studies reported in Fig. 1 and Table 1 were considered. The color of each node is a function of the number of studies monitoring the corresponding compartment, while each link represents the studies simultaneously monitoring the two compartments connected by the arrow. Since the focus of risk assessment are the two exposure sources DW and food, only the arrows directly connecting a compartment to the DW or food nodes were highlighted and colored with the same chromatic scale used for the nodes. For all the other links connecting different compartments black arrows were reported, distinguishing links for which no studies were found from links for which at least one study was found.

As indicated by the color of the links in Fig. 4, only limited knowledge is available on the transfer of both BPA and NP to tap water and food, with only 16 out of 42 studies investigating the origin of these contaminants in tap water, and only 6 out of 23 studies investigating the matrices that might have contributed to the accumulation of these contaminants in cereals, fruits and vegetables in real-world conditions. Moreover, no studies were found simultaneously monitoring BPA and NP in food and GW or TWW. Given the complex network of connections among all relevant environmental compartments, such lack of knowledge is detrimental, as it not only prevents the identification of the most relevant contamination pathways, but also restrains the potential to model the effect of alternative interventions. This limits the information available for intervention's prioritization. Thus, it is important to use the integrated procedure we proposed for risk assessment, to support the prioritization of future monitoring programs that are still needed to fill the knowledge gaps and collect useful data, when aiming at (i) better describe the fate of CECs in the whole system, (ii) assess the human health risk, and (iii) predict the effectiveness of the interventions in reducing such risk.

Finally, other factors such as food packaging (including water bottles) should be considered within the risk-based approach. In fact, most food packaging materials and processing equipment are made of plastics (i.e., polycarbonate, polyvinylchloride, polypropylene, polystyrene) or contain polymeric layers that are put in direct contact with food (i.e., epoxyphenolic resins coating metallic surfaces of food cans, caps of glass jars, paperboard lacquers) and contain several chemicals, including BPA and NP, which can migrate into food or water (Vilarinho et al., 2019). As an example, EFSA referred of an average BPA concentration in packaged foodstuff in Europe of about 10-fold higher than in unpackaged food (EFSA, 2015). Kawamura et al. observed a migration of NP from plastic wrap films into vegetables and fruit up to 2.9%–6.4% of the film content, corresponding to an NP intake rate of about 0.7 μg $kg^{-1}$ $day^{-1}$ (Kawamura et al., 2017).

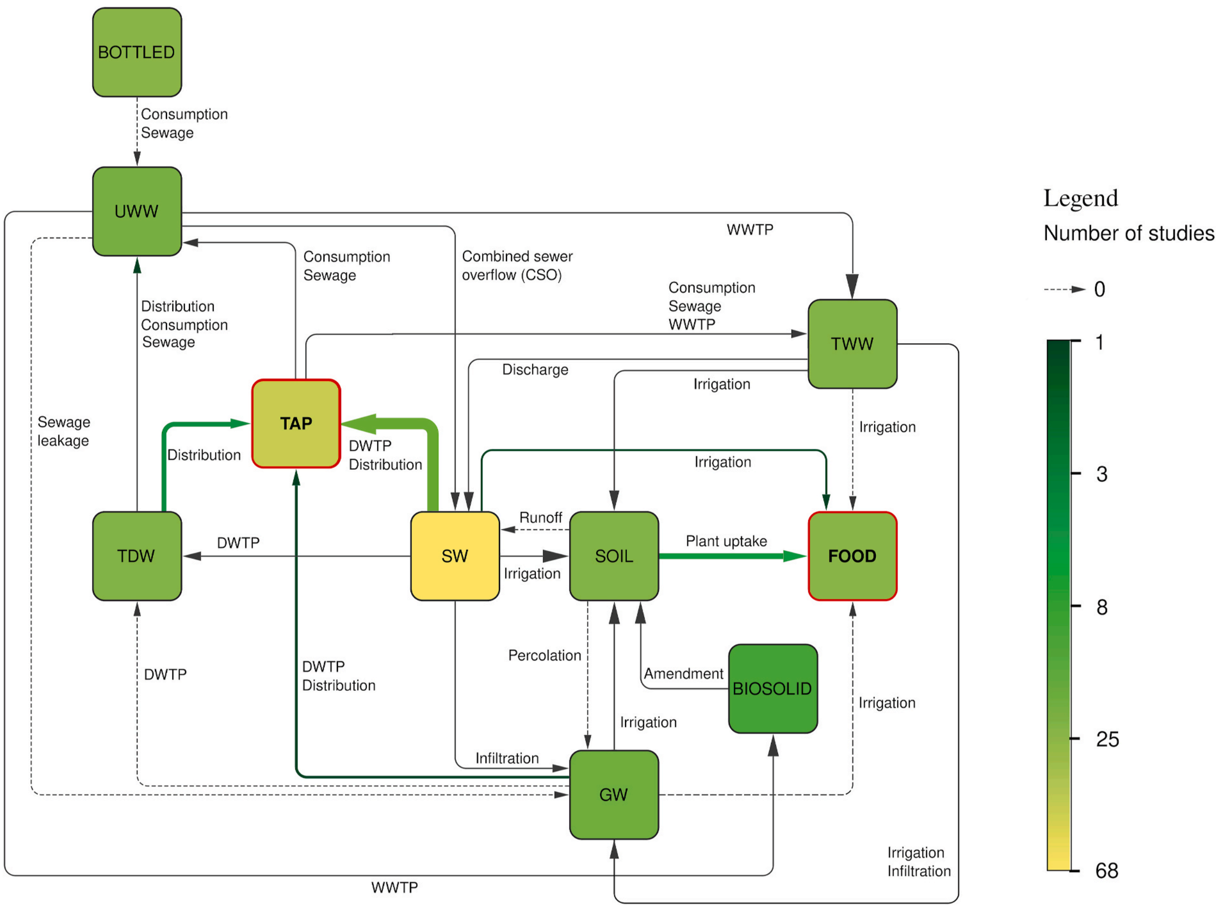



**Fig. 4.** Environmental compartments and cause-effect links investigated in literature for BPA and NP. Nodes and edges are color-coded depending on the number of literature studies investigating such compartment or link, with labels indicating either the compartment name or details regarding the nature of the link. Environmental compartments are framed in black, while the two exposure sources are framed in red. Dashed black arrows indicate links missing from literature (i.e. number of studies = 0). Diagram created with Cytoscape v3.9.1 (Shannon et al., 2003). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

## 4. Conclusions

Integrated quantitative risk assessment of CECs in a complex system including relevant interconnected compartments (groundwater, surface water, treated drinking water, consumed tap water, untreated wastewater, treated wastewater, biosolids, agricultural soil and unpacked fresh food, either as cereals or as fruit and vegetables) has proved to be an effective tool. Concerning the selected reference contaminants, namely BPA and NP, we remark the possibility of.

- identifying the proper LOQ of the analytical methods in order not to under- or over-estimate the risk due to improper use of data below the LOQ;
- identifying the main sources of human health risk and the apportionment of the different contributions; in the specific case, although the risk due to NP was not negligible, the calculated risk for human health due to BPA was significantly higher, and cereals and fruits and vegetables consumption determined a higher risk compared to tap water;
- exploring intervention strategies to be adopted to reduce the overall risk due to the exposure to the mixture of contaminants via multiple pathways;

In addition, the developed procedure might be useful in suggesting research directions to fill knowledge gaps in BPA and NP concentrations (and in general of CECs concentrations) in the different compartments. In fact, those concentrations are affected by very high variability resulting in high uncertainty in the estimated risk. Thus, the developed procedure might provide indications for future monitoring campaigns to better evaluate the CECs fate in different compartments simultaneously.

From this work, it emerges that more research efforts are needed in the field of assessing the impact of packaging materials on DW and food contamination, not accounted for in this paper, and to identify potentially dangerous by-products generated in the environment, which might cause different or additional risks. Moreover, it will be beneficial to systematically extend this developed procedure to other CECs to support the prioritization in wastewater treatments and also the identification of the more effective mitigation measures to prevent contamination of water and food intended for human consumption.

## Credit author statement

**Luca Penserini:** Methodology, Investigation, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; **Beatrice Cantoni**: Conceptualization, Methodology, Formal Analysis, Writing – Review & Editing; **Marco Gabrielli:** Validation, Visualization, Writing – Review & Editing, **Elena Sezenna:** Investigation, Validation, Writing – Review & Editing, **Sabrina Saponaro:** Supervision, Validation, Writing – Review & Editing, **Manuela Antonelli:** Supervision, Conceptualization, Writing – Review & Editing, Funding Acquisition.

## Funding

This study was carried out within the RETURN Extended Partnership and received funding from the European Union Next-GenerationEU (National Recovery and Resilience Plan – NRRP, Mission 4, Component 2, Investment 1.3 – D.D. 1243 2/8/2022, PE0000005).

## Declaration of competing interest

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.

## Data availability

Data will be made available on request.

## Acknowledgements

We are grateful to Acque Bresciane S. r.l., which manages the integrated water service for the province of Brescia, for supporting this work funding a PhD grant.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2023.138259.

## References

Bagheri, M., He, X., Oustriere, N., Liu, W., Shi, H., Limmer, M.A., Burken, J.G., 2021. Investigating plant uptake of organic contaminants through transpiration stream concentration factor and neural network models. Sci. Total Environ. 751, 141418 https://doi.org/10.1016/j.scitotenv.2020.141418.

Baken, K.A., Sjerps, R.M.A., Schriks, M., Wezel, A.P. Van, 2018. Toxicological risk assessment and prioritization of drinking water relevant contaminants of emerging concern. Environ. Int. 118, 293–303. https://doi.org/10.1016/j.envint.2018.05.006.

Cantoni, B., Cappello Riguzzi, A., Turolla, A., Antonelli, M., 2021a. Bisphenol A leaching from epoxy resins in the drinking water distribution networks as human health risk determinant. Sci. Total Environ. 783, 146908 https://doi.org/10.1016/j.scitotenv.2021.146908.

Cantoni, B., Delli Compagni, R., Turolla, A., Epifani, I., Antonelli, M., 2020. A statistical assessment of micropollutants occurrence, time trend, fate and human health risk using left-censored water quality data. Chemosphere 257, 127095. https://doi.org/10.1016/j.chemosphere.2020.127095.

Cantoni, B., Penserini, L., Vries, D., Dingemans, M.M.L., Bokkers, B.G.H., Turolla, A., Smeets, P.W.M.H., Antonelli, M., 2021b. Development of a quantitative chemical risk assessment (QCRA) procedure for contaminants of emerging concern in drinking water supply. Water Res. 194, 116911 https://doi.org/10.1016/j.watres.2021.116911.

Careghini, A., Mastorgio, A.F., Saponaro, S., Sezenna, E., 2015. Bisphenol A, nonylphenols, benzophenones, and benzotriazoles in soils, groundwater, surface water, sediments, and food: a review. Environ. Sci. Pollut. Res. 3, 49–58. https://doi.org/10.1007/s11356-014-3974-5.

Christou, A., Papadavid, G., Dalias, P., Fotopoulos, V., Michael, C., Bayona, J.M., Piña, B., Fatta-Kassinos, D., 2019. Ranking of crop plants according to their potential to uptake and accumulate contaminants of emerging concern. Environ. Res. 170, 422–432. https://doi.org/10.1016/j.envres.2018.12.048.

de Bruin, W., Kritzinger, Q., Bornman, R., Korsten, L., 2019. Occurrence, fate and toxic effects of the industrial endocrine disrupter, nonylphenol, on plants - a review. Ecotoxicol. Environ. Saf. 181, 419–427. https://doi.org/10.1016/j.ecoenv.2019.06.009.

Delli Compagni, R., Gabrielli, M., Polesel, F., Turolla, A., Trapp, S., Vezzaro, L., Antonelli, M., 2020. Risk assessment of contaminants of emerging concern in the context of wastewater reuse for irrigation: an integrated modelling approach. Chemosphere 242, 125185. https://doi.org/10.1016/j.chemosphere.2019.125185.

EFSA, 2021. Re-evaluation of the risks to public health related to the presence of bisphenol A 4 (BPA) in foodstuffs (Draft). EFSA J. 1–428.

EFSA, 2015. Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs. EFSA J. 13 https://doi.org/10.2903/j.efsa.2015.3978.

EFSA, 2011. Use of the EFSA comprehensive European food consumption Database in exposure assessment. EFSA J. 9, 1–34. https://doi.org/10.2903/j.efsa.2011.2097.

European Commission, 2022. Commission Implementing Decision Establishing a Watch List of Substances and Compounds of Concern for Water Intended for Human Consumption as provided for in Directive (EU) 2020/2184 of the European Parliament and of the Council. https://Medium.Com/1-2.

European Commission, 2018. DIRECTIVE OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the quality of water intended for human consumption. recast) 53, 1689–1699.

European Commission, 2016. COMMISSION REGULATION (EU) 2016/2235 of 12 december 2016 amending annex XVII to regulation (EC) No 1907/2006 of the European parliament and of the council concerning the registration, evaluation, authorisation and restriction of chemicals (REACH) as regar. Off. J. Eur. Union 2001, 20–30.

European Commission, U, 2020. Directive (EU) 2020/2184 of the European parliament and of the council. Off. J. Eur. Union 2019, 1–62.

Gogoi, A., Mazumder, P., Tyagi, V.K., Tushara Chaminda, G.G., An, A.K., Kumar, M., 2018. Occurrence and fate of emerging contaminants in water environment: a review. Groundw. Sustain. Dev. 6, 169–180. https://doi.org/10.1016/j.gsd.2017.12.009.

Guerra, P., Kim, M., Teslic, S., Alaee, M., Smyth, S.A., 2015. Bisphenol-A removal in various wastewater treatment processes: operational conditions, mass balance, and optimization. J. Environ. Manag. 152, 192–200. https://doi.org/10.1016/j.jenvman.2015.01.044.

Hahladakis, J.N., Iacovidou, E., Gerassimidou, S., 2022. An overview of the occurrence, fate, and human risks of the bisphenol-A present in plastic materials, components, and products. Integrated Environ. Assess. Manag. 1–18. https://doi.org/10.1002/ieam.4611.

Helsel, D.R., 2012. Statistics for Censored Environmental Data Using MINITAB® and R, second ed. John Wiley & Sons, New Jersey.

IPCC, 2022. Climate change 2022: impacts, adaptation and vulnerability working group II contribution to the IPCC sixth assessment report citations to the sixth assessment report of the intergovernmental panel on climate change [ to the sixth assessment report of the. https://doi.org/10.1017/9781009325844 (Front).

Kawamura, Y., Ogawa, Y., Mutsuga, M., 2017. Migration of nonylphenol and plasticizers from polyvinyl chloride stretch film into food simulants, rapeseed oil, and foods. Food Sci. Nutr. 5, 390–398. https://doi.org/10.1002/fsn3.404.

Kummu, M., Guillaume, J.H.A., de Moel, H., Eisner, S., Florke, M., Porkka, M., Siebert, S., Veldkamp, T.I.E., Ward, P.J., 2016. The world's road to water scarcity: shortage and stress in the 20th century and pathways towards sustainability. Nature. https://news.ge/anakliis-porti-aris-qveynis-momava.

Lu, J., Wu, J., Stoffella, P.J., Wilson, P.C., 2015. Uptake and distribution of bisphenol A and nonylphenol in vegetable crops irrigated with reclaimed water. J. Hazard Mater. 283, 865–870. https://doi.org/10.1016/j.jhazmat.2014.10.018.

Luo, S., Li, Yun, Li, Yingpei, Zhu, Q., Jiang, J., Wu, C., Shen, T., 2016. Gestational and lactational exposure to low-dose bisphenol A increases Th17 cells in mice offspring. Environ. Toxicol. Pharmacol. 47, 149–158. https://doi.org/10.1016/j.etap.2016.09.017.

Muncke, J., 2021. Tackling the toxics in plastics packaging. PLoS Biol. 1–11. https://doi.org/10.1371/journal.pbio.3000961.

Penserini, L., Cantoni, B., Vries, D., Turolla, A., Smeets, P.W.M.H., Bokkers, B.G.H., Antonelli, M., 2022. Quantitative chemical risk assessment for mixtures: application to alkylphenol mixtures and phthalate mixtures in tap and bottled water. Environ. Int. 165, 107294 https://doi.org/10.1016/j.envint.2022.107294.

R Core Team, 2022. R: a language and environment for statistical computing [WWW Document]. URL. https://www.r-project.org/. accessed 9.30.22.

Rashtian, J., Chavkin, D.E., Merhi, Z., 2019. Water and soil pollution as determinant of water and food quality/contamination and its impact on female fertility. Reprod. Biol. Endocrinol. 17, 1–13. https://doi.org/10.1186/s12958-018-0448-5.

Revitt, D.M., Lundy, L., Fatta-Kassinos, D., 2021. Development of a qualitative approach to assessing risks associated with the use of treated wastewater in agricultural irrigation. J. Hazard Mater. 406, 124286 https://doi.org/10.1016/j.jhazmat.2020.124286.

Schriks, M., Heringa, M.B., , Kooi, M.M.E. Van Der, Voogt, P., De, Wezel, A.P. Van, 2010. Toxicological relevance of emerging contaminants for drinking water quality. Water Res. 44, 461–476. https://doi.org/10.1016/j.watres.2009.08.023.

Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T., Ramage, D., 2003. Nada amin, 2, benno schwikowski, 1, 5 and trey Ideker2, 3, 4, 5, 山本隆久, 豊田直平, 深瀬吉邦, 大森敏行. Cytoscape: A Software Environment for Integrated Models. Genome Res 13, 426. https://doi.org/10.1101/gr.1239303.metabolite.

Torres-García, J.L., Ahuactzin-Pérez, M., Fernández, F.J., Cortés-Espinosa, D.V., 2022. Bisphenol A in the environment and recent advances in biodegradation by fungi. Chemosphere 303. https://doi.org/10.1016/j.chemosphere.2022.134940.

Vilarinho, F., Sendón, R., van der Kellen, A., Vaz, M.F., Silva, A.S., 2019. Bisphenol A in food as a result of its migration from food packaging. Trends Food Sci. Technol. 91, 33–65. https://doi.org/10.1016/j.tifs.2019.06.012.

Westerhoff, P., Yoon, Y., Snyder, S., Wert, E., 2005. Fate of endocrine-disruptor, pharmaceutical, and personal care product chemicals during simulated drinking water treatment processes. Environ. Sci. Technol. 39, 6649–6663. https://doi.org/10.1021/es0484799.

WHO, 2017. Guidelines for Drinking-Water Quality.

WHO, 2006. WHO guidelines for drinking-water quality. Water Supply 11, 1–16.