A quantitative chemicals' mixture risk assessment approach for contaminants of emerging concern management in drinking water

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Abstract
Uncertainties on occurrence and hazard of mixtures of Contaminants of Emerging Concern (CECs) in drinking water (DW) challenge water utilities and decision makers in prioritizing these compounds in, respectively, interventions for the optimization of DW treatment and DW regulations. Continuous development of quantitative risk assessment procedures addressing adverse effects of CECs supports decision-making regarding mitigation actions in minimizing health risks. We propose a novel, quantitative chemical risk assessment (QCRA) approach for mixtures of CECs in DW. The risks are evaluated with the aid of the benchmark quotient probabilistic distribution and including uncertainties in both (i) exposure assessment using occurrence data of different DW sources and simulating DW treatment by granular activated carbon and (ii) hazard assessment steps. The QCRA was applied to compare risks deriving from the presence of alkylphenols mixtures in tap or bottled DW, and to evaluate how actual DW consumption habits affect health risks.

Keywords
Activated Carbon Adsorption; Contaminants of Emerging Concern (CEC); Drinking Water; Mixture Risk Assessment; Stochastic Modelling; Water Consumption Patterns.

INTRODUCTION

A large number of Contaminants of Emerging Concern (CECs) is present in water. Differences in their adverse effects on human health create the need for CECs prioritization based on risk levels in both (i) regulation in drinking water (DW) and (ii) treatment and monitoring interventions oriented at the optimization of DW supply system (Cantoni et al., 2021). A risk assessment procedure can address this need, but some issues should be considered. For the exposure assessment, exposure concentrations (C_{EXP}) data are often lower than the analytical limit of quantification which leads to censored data. In addition, knowledge gaps are present on CECs fate throughout DW treatment, such as for granular activated carbon (GAC) treatment. For the hazard assessment, health-based values, namely Drinking Water Target Levels (DWTLs), are not derived for every CEC yet, as toxicological studies on CECs can be indecisive and, in some cases, confidential. Therefore, a robust risk assessment should account for these uncertainties.

Health risk for compounds mixtures in DW is conventionally estimated based on deterministic chemical risk assessment (CRA), adopting the Hazard Index (HI) approach: for each single selected compound, the deterministic benchmark quotient (BQ) is calculated as the ratio between point values of its highest C_{EXP} and its lowest DWTL. By summing up all the individual BQs, the HI is finally obtained, assuming the principle of dose addition without considering the specific endpoint that each compound affects (Baken et al., 2018). A more refined approach for mixtures risk assessment is based on the Relative Potency Factors (RPF), in which only those compounds affecting the same endpoint are added and their concentrations are expressed as equivalents of a reference compound based on their potencies, before being summed (Bil et al., 2021).

In previous work, Cantoni et al. (2021) developed a new quantitative chemical risk assessment (QCRA) procedure for the probabilistic quantification of the health risk due to the presence of

single CECs in DW, where a probabilistic BQ was estimated by replacing point values of maximum C_{EXP} and DWTL with their statistical distributions. The QCRA procedure was applied to explore the effects of different operational modes of GAC treatment on health risk on bisphenol-A (BPA) as reference CEC. In this work, the QCRA procedure was extended with the RPF approach to allow estimation of the risk associated to mixtures of compounds. In particular, due to their presence in bottled and tap water, alkylphenols were investigated, i.e., BPA, nonylphenol (NP) and octylphenol (OP). The mixture-extended QCRA procedure was applied to compare the risks related to the consumption of bottled and tap DW. In addition, actual water consumption data were evaluated to assess the influence of DW consumers' behaviour on the estimated risk.

MATERIALS AND METHODS

In the hazard assessment step RPFs and DWTL distributions were quantified for alkylphenols (affected endpoint: kidney). RPFs for NP and OP were estimated comparing their dose-response curves to the one of BPA, selected as reference compound. RPFs were applied to their C_{EXP} to convert them into equivalent concentrations corresponding to the reference contaminant. Resulting equivalent concentrations are then summed up to obtain the mixture concentration (C_{MIX}), as:

$$C_{MIX} = C_{EXP,REF} + \sum_i (C_{EXP,i} \times RPF_i) \quad (1)$$

where $C_{EXP,REF}$ [μg_{REF} L^{-1}] is the reference compound (BPA) C_{EXP}, and $C_{EXP,i}$ [μg_i L^{-1}] and RPF_i [μg_{REF} μg_i^{-1}] represent respectively the C_{EXP} and the RPF of the *i-th* compound. DWTLs represent the compound dose that does not result in the exceedance of the tolerable oral exposure of a DW consumer over lifetime. The $DWTL_{REF}$ [$\mu g\ kg^{-1}\ day^{-1}$] was calculated as:

$$DWTL_{REF} = \frac{PoD_{REF}}{AF} \times P \quad (2)$$

where PoD_{REF} [$mg\ kg^{-1}\ day^{-1}$] is the reference compound Point of Departure, AF is the Assessment Factor and P is the allocation factor, namely the percentage of risk associated to DW consumption compared to all the exposure pathways (constant and equal to 20%). BPA toxicological data were collected from the most recent toxicological scientific opinion (EFSA, 2015). To derive DWTL uncertainty distribution, the APROBA-Plus tool was used, as described by Bokkers et al. (2017).

For the exposure assessment step, C_{EXP} data from raw, tap and bottled water were collected from literature; GAC-treated water data were obtained by modelling GAC filtration breakthrough curves as in Cantoni et al. (2021). C_{EXP} statistical distributions were estimated and combined in C_{MIX} following Eq. 1. Then, the mixture equivalent dose, $Dose_{MIX}$ [$mg\ kg^{-1}\ day^{-1}$] was derived as:

$$Dose_{MIX} = C_{MIX} \times WIR \quad (3)$$

where WIR is the Water Intake Rate [$L\ kg^{-1}\ day^{-1}$], that is the ratio between daily DW consumption (DWC) and body weight (constant and equal to 60kg). DWC was first set as a constant value (2 $L\ day^{-1}$) and then estimated from real DW consumption data collected from worldwide literature.

For the risk characterization step, the statistical distributions obtained for $DWTL_{REF}$ and for alkylphenols $Dose_{MIX}$, for bottled and tap water, were used to sample 1,000 data each, from which the corresponding series of 1,000 BQ_{MIX} values were computed as:

$$BQ_{MIX} = \frac{Dose_{MIX}}{DWTL_{REF}} \quad (4)$$

which were employed to extrapolate three different data: the maximum probabilistic BQ_{MIX} ($BQ_{PROB,MAX}$), corresponding to 99th percentile of the fitted BQ_{MIX} distribution, the probability of BQ_{MIX} above the health risk threshold values equal to 1 ($P(BQ_{MIX}>1)$), and equal to 0.1 ($P(BQ_{MIX}>0.1)$). For uncertainty analysis, Monte Carlo simulation method (n=1,000) was applied with the simultaneous forward propagation of the uncertainties of all the relevant inputs.

RESULTS AND DISCUSSION

A schematic overview of the developed QCRA procedure for mixtures is reported in Figure 1.

RPF analysis highlighted that both NP and OP are three times more potent than BPA with respect to effects on relative kidney weight. RPF factors, which are proxy variables of the compounds' toxicological characterization, enabled to upgrade the original QCRA, designed for single CECs, into a procedure capable of properly assessing mixtures of CECs, where associated risks may be

higher due to additive effects and hence may lead to greater toxicity.

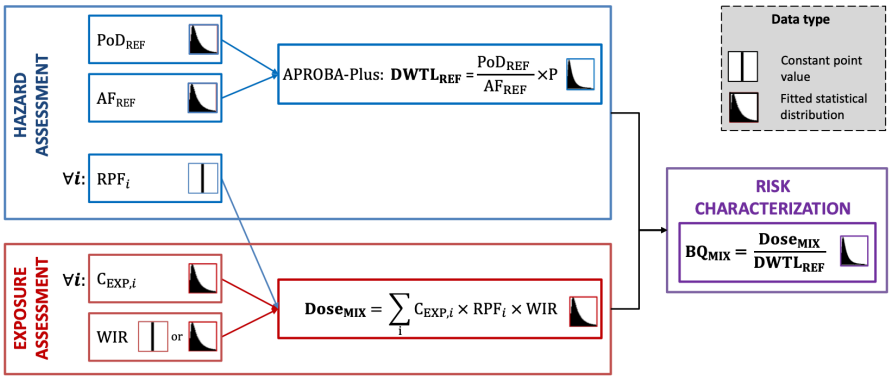

Figure 1. Schematic overview of the framework for the QCRA implementation for compounds mixture: modelling steps, input and output variables, and their statistical distributions.

As for the $DWTL_{REF}$, the greatest contributor to its uncertainty is the AF accounting for intraspecies differences, with 28% contribution, followed by the duration extrapolation factor (25%) and the uncertainty on the PoD (20%). In contrast to a deterministic CRA where a BQ point value is estimated, QCRA yields a probability distribution providing more insights on its reliability. The QCRA is applied to three scenarios of CECs mixtures to illustrate the approach. In the first two, DW consumption is assumed to be totally based on bottled water (scenario: BOTTLED), and on tap water (scenario: TAP), to compare bottled and tap water in terms of health risk associated to alkylphenols. For both scenarios, DWC was assumed to be constant and equal to 2 L day^{-1}.

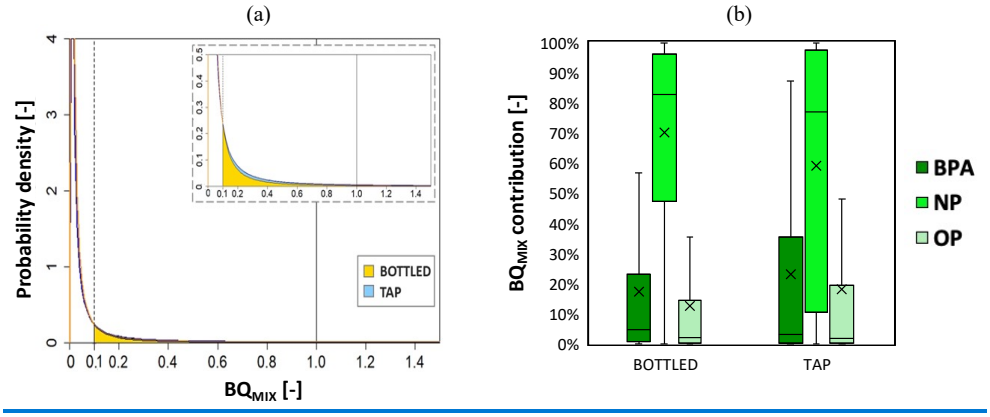

Figure 2: (a) BQ_{MIX} probability density of bottled and tap water for alkylphenols. (b) Alkylphenols percentage contribution to the BQ_{MIX} for bottled and tap water.

To properly evaluate the probabilistic QCRA results (Figure 2) when a chronic effect is analysed, as it can be the case for the presence of CECs in DW, $P(BQ_{MIX}>1)$ and $P(BQ_{MIX}>0.1)$ are the most appropriate parameters, indicating the probability that the DW consumer would drink respectively contaminated water ($BQ_{MIX}>1$) and water which needs further investigation to understand if a toxic effect can be effectively displayed ($BQ_{MIX}>0.1$). In this case, QCRA highlights that the consumption of both tap and bottled water results to be a potential health risk determinant for alkylphenols, having $BQ_{PROB,MAX}$ values higher than 1 and a $P(BQ_{MIX}>1)$ equal to, respectively 0.47% to 0.06%. Moreover, further investigations are needed for both tap and bottled waters since $P(BQ_{MIX}>0.1)$ is equal to, respectively 3.26% to 1.49%. Moreover, single compounds contribution to overall BQ_{MIX} (Figure 2b) confirmed what emerged from RPF analysis: although NP C_{EXP} distribution is similar to BPA's one, NP is the main contributor to the overall risk due to its toxicological characteristics. Thus, it is fundamental to prioritize CECs based on their risk contribution and not only on their exposure concentrations levels.

In the third scenario, it has been evaluated how DW consumption habits affect the health risk considering real data on total DW consumption and fractions of bottled and tap water for different countries. From the collected country-related water consumption dataset, three clusters of countries were identified (CL-1, CL-2 and CL-3), representative of different DW consumption habits.

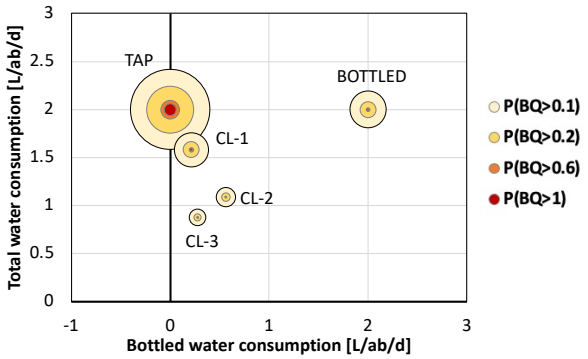

Figure 3: Bubble charts with bubble diameters proportional to the probability of BQ_{MIX} exceeding different risk thresholds. Total water consumption is intended as the sum of bottled and tap water.

In Fig. 3 each bubble corresponds to a particular scenario and the bubble centres are located according to their mean values for the total water consumption (y-axis) and bottled water consumption (x-axis). CL-1, characterized by the countries with the highest total DW consumption, shows a higher risk compared to other clusters (CL-1 > CL-3 ~ CL-2), with a $P(BQ_{MIX}>0.1)$ equal respectively to 1.39, 0.65 and 0.79. This trend is proportional to the total water consumption and, thus, the risk is mainly influenced by the amount of consumed DW rather than on the type of water, since tap and bottled waters have similar BQ_{MIX} distributions (Fig. 2). These findings point out that considering the actual water consumption data, could lead to a different and more realistic risk estimation, and that it is essential to consider this aspect for a more accurate risk assessment.
Our work highlighted the potential of a mixture-extended QCRA as a method to determine the contribution of various actions in reducing health risk, and can therefore be useful for prioritization of both interventions in the whole DW supply system, as well as in CECs regulations.

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