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Quantitative chemical risk assessment for mixtures: Application to alkylphenol mixtures and phthalate mixtures in tap and bottled water

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ABSTRACT

The occurrence and hazard risks of mixtures of Contaminants of Emerging Concern (CECs) in drinking water (DW) lead to serious consideration regarding the possible impacts on public health. Consequently, there is ongoing research, development and empowerment of risk assessment procedures to get more toxicological insight. For instance, alkylphenols and phthalates have been frequently reported to be present both in bottled and tap water, affecting different human endpoints. Currently, deterministic chemical risk assessment (CRA) is used to evaluate the compounds' mixture health risk. However, CRA deals just qualitatively with sources of uncertainty, which may lead to erroneous assessment of risks. Here, a new procedure for quantitative chemical risk assessment of CEC mixtures ($QCRA_{MIX}$) is proposed. Its potential is illustrated by a case study where the risks related to the presence of mixtures of alkylphenols or phthalates in tap versus bottled DW are compared. Uncertainties in both exposure and hazard assessment steps of the procedure are included to calculate a probabilistic mixture Benchmark Quotient (BQ_{MIX}). The $QCRA_{MIX}$ procedure highlighted the non-negligible health risks posed by those compounds in both DW sources based on overall water consumption. In fact, DW consumers' behaviour in 13 different countries, in terms of total DW consumption and fraction of bottled and tap water consumed, were considered to evaluate the influence on health risk. For alkylphenols, the total water consumption was found to be the most relevant factor in increasing the health risk, while for phthalates the risk was found to be mainly influenced by the percentage of bottled water consumed. Hence, the proposed $QCRA_{MIX}$ procedure can be a valuable tool for prioritization of CECs to be included in DW regulations which aim to minimize the overall risk, accounting for actual DW consumption.

1. Introduction

Health risks due to the presence of Contaminants of Emerging Concern (CECs) in drinking water (DW) lead to growing interest (Mao et al., 2019). CECs are a heterogeneous group of compounds of anthropogenic origin (e.g., alkylphenols, pharmaceuticals, microplastics), which are commonly present as mixtures in water and, despite the low concentrations detected, they can cause adverse human health chronic effects (Baken et al., 2018). In fact, even if all the mixture components are present at levels that individually would not cause observable effects, humans can be adversely affected as a result of the chronic exposure to low amounts of mixtures of CECs, which may act additively to induce greater toxicity (Altenburger et al., 2018). For CECs, oral intake is the primary exposure pathway, and DW is one of the major sources (Li et al., 2018). As reviewed by Akhbarizadeh et al. (2020), many studies reported the presence of two main groups of contaminants in DW, both in bottled and tap water, namely alkylphenols and phthalates. Plastic bottled water can be contaminated in different phases of the production and distribution chain, from supplying of the materials to handling and storage, considering that storage conditions enhance contaminants migration into water (Luo et al., 2018). As for tap water, contamination can be already present due to (i) background contamination before entering the drinking water distribution network (DWDN), or due to (ii) leaching of chemicals from pipe materials within the DWDN in high residence time settings (Cantoni et al., 2021a).

For deterministically quantifying the risks of chemicals mixtures in

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DW, a chemical risk assessment (CRA) procedure is usually applied by using the Hazard Index (HI) approach. The HI is calculated by summing up the individual Benchmark Quotients (BQs) of all the considered compounds, where each BQ is the ratio between the single compound exposure and its Drinking Water Target Level (DWTL), or health-based guidance value (HBGV). If the HI is lower than 1, the risk for human health due to the co-exposure to the evaluated compounds is considered negligible (WHO, 2010). The deterministic HI approach was applied in several studies over the last years: for example Riva et al. (2018) assessed the cumulative health risk due to the co-exposure to several CECs in tap water, including alkylphenols, as well as different studies evaluated the health risk due to single phthalates (Jeddi et al., 2015), or to mixtures of them (Liu et al., 2015), in both bottled and tap water.

Furthermore, risks resulting from different compounds are summed independently from the specific endpoint they affect, assuming the principle of dose addition. Consequently, compounds capability to affect the same endpoint, which could magnify the risk, is neglected (Bosgra et al., 2009). A more refined approach for the risk assessment of compounds mixtures is by using Relative Potency Factors (RPFs), in which only those compounds affecting the same endpoint are added and their concentrations are expressed as equivalents of one reference compound, before being summed (Bil et al., 2021).

In general, a deterministic CRA does not take quantitatively into account the uncertainties inevitably associated to measurement of CEC concentrations (Bokkers et al., 2017). Moreover, the majority of CECs DWTLs in toxicological characterization have not been derived yet and thus DWTL values are not always reliable or available due to contradictory and confidential toxicological studies (Baken et al., 2018). Therefore, a stochastic approach for the health risk estimation of CECs is highly beneficial. However, few case studies providing a probabilistic quantification of the risk are reported in literature, typically including the uncertainty analysis just in one single aspect of the risk assessment, as in the exposure assessment (Thomaidi et al., 2020), or in the hazard assessment (Chiu and Slob, 2015).

To overcome these issues, Cantoni et al. (2021b) proposed a new quantitative chemical risk assessment (QCRA) procedure for the probabilistic quantification of the health risk due to the presence of a single CEC in DW. In this assessment, a probabilistic BQ was estimated by replacing point values of maximum exposure concentration (C_{EXP}) and minimum DWTL with their statistical distributions. This enabled quantifying the robustness of the estimated risk and the main sources of uncertainty.

The aim of this work, is to extend the QCRA procedure by using RPFs to estimate the risk associated to mixtures of contaminants, as well as retaining the quantification of uncertainties. A new procedure is proposed, called quantitative chemical risk assessment for mixtures ($QCRA_{MIX}$), which aims at estimating the risk in terms of mixture BQ (BQ_{MIX}) to assess risks of multiple contaminants based on the specific affected endpoint. To the best of the authors' knowledge, no such research studies which evaluate the probabilistic health effects of mixtures of CECs in the field of DW are reported yet. The proposed framework was applied to alkylphenols mixtures and phthalates mixtures, due to their frequent presence in bottled and tap water and their toxicological data consistency and availability.

Three scenarios were considered for the application of the newly developed $QCRA_{MIX}$ procedure. In the first two the risks related to the consumption of bottled and tap water were compared, considering a constant daily water consumption. In the third case, actual water consumption data were evaluated to assess the influence of DW consumers' behaviour (total amount of consumed DW and relative consumption of tap and bottled water) on the estimated risk.

2. Materials and methods

2.1. Quantitative chemical risk assessment for mixtures ($QCRA_{MIX}$) modelling

A probabilistic modelling framework was defined for the development of the $QCRA_{MIX}$ (Fig. 1). It consists of three steps: (i) in the hazard assessment, DWTLs distributions and RPFs are derived from dose-response data obtained from available toxicological studies; (ii) in the exposure assessment, the mixture dose ($Dose_{MIX}$) distribution is derived from the combined mixture concentration (C_{MIX}) and Water Intake Rate (WIR) distributions, and (iii) in the risk characterization, results from previous steps are combined to obtain the BQ_{MIX} distribution.

2.1.1. Hazard assessment

This step deals with the quantitative characterization of the considered compounds' adverse health effects (WHO, 2017). To evaluate the cumulative risk resulting from the exposure to a mixture, it is necessary firstly to identify the common critical endpoint, and secondly to quantify the associated adverse health effect due to DW consumption (Bosgra et al., 2009). The common critical endpoint of alkylphenols is decreased kidney weight (EFSA, 2015), which is observed after exposure to bisphenol A (BPA), nonylphenol (NP) and octylphenol (OP). For phthalates the common critical effect is reproductive toxicity (EFSA, 2019) observed from bis-(2-ethylhexyl) phthalate (DEHP), di-butyl phthalate (DBP), di-isobutyl phthalate (DiBP) and benzyl butyl phthalate (BBP). The physicochemical properties of the considered compounds are reported in Table S1, in the Supplementary Materials (SM).

2.1.1.1. RPFs determination. RPFs are factors to be applied to the C_{EXP} of a set of compounds to convert them into equivalent concentrations corresponding to a reference contaminant. Resulting equivalent concentrations can be then summed up to obtain the C_{MIX}, as in Eq. (1) (Bil et al., 2021):

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

where C_{MIX} [$\mu g_{REF}\ L^{-1}$] is expressed in equivalents of the reference compound, $C_{EXP,REF}$ [$\mu g_{REF}\ L^{-1}$] is the reference compound C_{EXP}, and $C_{EXP,i}$ [$\mu g_i\ L^{-1}$] and RPF_i [$\mu g_{REF}\ \mu g_i^{-1}$] represent respectively the C_{EXP} and the RPF of the *i-th* compound.

The evaluated compounds must affect the same endpoint to allow the evaluation of a cumulative risk index. For this reason, the mixture risks for the group of three alkylphenols and for the group of the four phthalates are estimated separately. Moreover, the RPF approach requires other conditions to be satisfied. Firstly, toxicological data for the RPF estimation should be obtained from studies with similar experimental setups (species, sex, generation, exposure route and duration), to avoid that differences in experimental setups influence the RPF estimation. Secondly, the mixture components should show parallel dose–response curves on a log scale, to have constant RPF over the range of effects. Lastly, the mixture components should not interact, because, in case of interaction, dose–response information of the individual contaminants are not sufficient to predict their combined effects. When these conditions are met, the RPFs can be derived following Eq. (2) (Bosgra et al., 2009):

$$RPF_i = \frac{BMD_{X,\,REF}}{BMD_{X,\,i}} \quad (2)$$

where BMD_X [mg $kg_{body\ wt}^{-1}\ day^{-1}$] indicates the benchmark dose corresponding to a benchmark response of a (relative) change in response of X%. For the RPF estimation, it is required that the two benchmark doses (one for the reference compound and one for *i-th* compound) are equipotent, i.e., they should cause the same change in response (of X%).

The toxicological studies on the alkylphenols used were previously

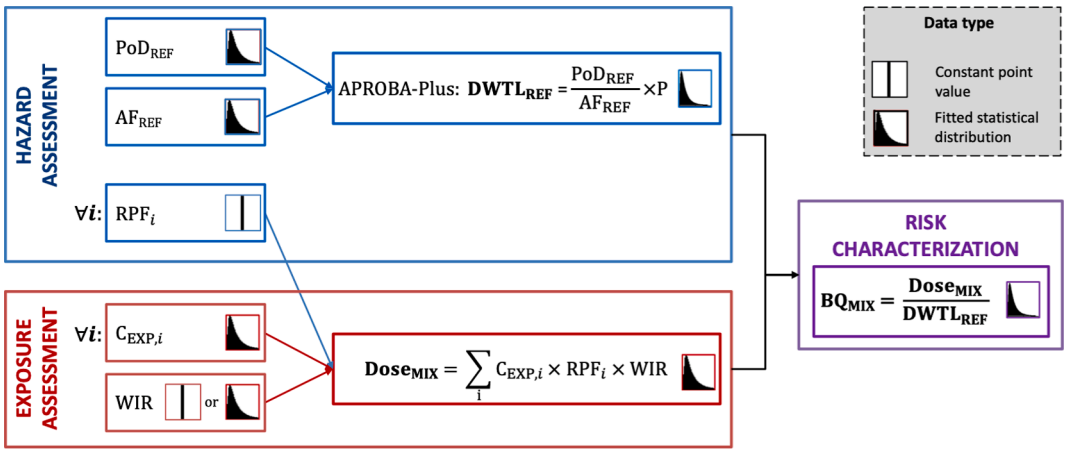

Fig. 1. Schematic overview of the newly developed framework for $QCRA_{MIX}$ implementation: modelling steps, input and output variables, and their statistical distributions.

selected by the European agencies responsible for the risk assessment of these substances, i.e. EFSA and ECHA. Since for BPA a risk assessment was already provided by EFSA (2015), it was selected as reference compound. EFSA's scientific opinion on BPA identified the alteration of mean relative kidney weight [$g_{organ\ wt}\ kg^{-1}_{body\ wt}$] as critical chronic effect; hence, it was assumed as response for this group of compounds. For BPA, NP and OP, being the only alkylphenols frequently detected in DW, toxicological studies were collected from ECHA website (https://echa.europa.eu/information-on-chemicals), and critically reviewed to select the ones with similar experimental setups. Thus, data were obtained from studies with the same species (rat), sexes (male and female), generations (F0, F1, F2 and F3), exposure route (oral) and comparable exposure durations (4–10 weeks). Among all the collected toxicological studies, the ones with similar setups are: Tyl et al. (2002) for BPA, Chapin et al. (1999) and Tyl et al. (2006)for NP, and Bayer (1982, as referred to on the ECHA website) for OP. A summary of the selected toxicological studies experimental setups is reported in Table S2. PROAST software, v.70.2 (RIVM, 2021) was used for dose–response curves modelling to verify whether dose–response data could be described by parallel curves (on a log dose scale) and to estimate RPFs, as indicated in Eq. (2). For more details on the dose–response modelling, see SM Section 2.

A review of the toxicological data on phthalates identified testes effects as the common critical endpoint (EFSA, 2019). DEHP was selected as the reference compound, for the robustness of its related toxicological data. Among all the analysed phthalates, DEHP, DBP, BBP and DiBP were included in the analysis. Other phthalates were discarded because they (i) affected different critical endpoints, (ii) lacked sufficient toxicological data, or (iii) DW concentration data. The reasons for discarding compounds are further detailed in Table S3. However, although all the selected compounds presented effects on testes, the available toxicological studies provided different metrics of the testis effects, which hampered deriving the equipotent doses required in the RPFs calculation. Therefore, EFSA calculated the RPFs using HBGVs as equipotent doses. For DEHP, DBP, BBP, the RPFs published by EFSA were used. In addition, we aimed at deriving RPFs of DiBP, which is also present in water, and which also causes testis effects. In particular, Hannas et al. (2011) was considered as reference study. A description of the selected toxicological studies on phthalates is reported in Table S2.

2.1.1.2. DWTLs determination. A crucial goal for the hazard assessment step is the estimation of a health-based value, the DWTL, which represents the dose of a compound that does not result in exceeding the tolerable oral exposure of a DW consumer over lifetime (WHO, 2010). For each reference compound, the $DWTL_{REF}$ [$\mu g\ kg^{-1}\ day^{-1}$] was calculated by Eq. (4) (Baken et al., 2018):

$$DWTL_{REF} = \frac{PoD_{REF}}{AF} \times P \quad (4)$$

where PoD_{REF} [$mg\ kg^{-1}\ day^{-1}$] is the Point of Departure for the reference compound, AF is the Assessment Factor and P [%] is the allocation factor, namely the percentage of risk maximally associated to DW consumption compared to the overall exposure pathways, considered as constant and equal to 20% (Baken et al., 2018). For the PoD estimations, toxicological data were collected from the most recent toxicological scientific opinions available, published by EFSA (2015) for BPA and by EFSA (2019) for DEHP.

For BPA, EFSA identified the mean relative kidney weight from the F1 males in a two-generation toxicity study in mice (Tyl et al., 2008) as the critical effect of BPA. Starting from this study, BPA DWTL uncertainty distribution, which aims to protect 99% of the population to 5% (or more) decrease in relative kidney weight was obtained by using the APROBA-Plus tool, following the same assumptions and methods already explained in Cantoni et al. (2021b). From this distribution a probabilistically estimated DWTL can be derived covering 95% of its estimation uncertainty. The adopted parameters and assumptions for BPA's DWTL determination are reported in Table S4 and Table S5.

Regarding DEHP, the toxicological study indicated by EFSA was Wolfe and Layton (2005), evaluating three-generation reproductive toxicity on rats, through the analysis of testes effects in F1 and F2 generations. The PoD that EFSA identified from the study was a NOAEL (No Observed Adverse Effect Level) equal to 4.8 $mg\ kg^{-1}\ day^{-1}$ based on critical effects for small reproductive organs and testis atrophy. EFSA applied a default AF value of 100 to the identified NOAEL to account for possible inter- and intraspecies differences. This resulted in a deterministic oral HBGV of 50 $\mu g\ kg^{-1}\ day^{-1}$. In this case, being the critical effect a reprotoxic effect, there was no need to apply a duration extrapolation factor for subchronic-to-chronic conversion. Again, to derive DWTL uncertainty distribution the APROBA-Plus tool was used, as described by Bokkers et al. (2017), by adopting the default lower and upper bound values suggested by the APROBA-Plus Tool for NOAEL-to-BMD conversion, interspecies, and intraspecies, reported in detail in Table S8 and Table S9.

2.1.2. Exposure assessment

This step addresses the quantification of route, magnitude and frequency of exposure to the considered compounds (WHO, 2017).

In these paragraphs, it is explained how $Dose_{MIX}$ distribution to which DW consumers are exposed were quantified, starting from C_{MIX} and WIR statistical distributions.

2.1.2.1. Exposure concentration data collection. The relevant route of

exposure was ingestion of bottled and tap water. Maximum concentration data were collected from literature studies analysing bottled and tap waters worldwide. For bottled water, only data related to PET bottles, analysed right after their purchase (i.e., without considering data from storage condition experiments) were used.

For each compound, the number of available data, their associated statistical summary data and references are reported in Table 1, while more detailed information about the references are shown in Table S12.

Collected data were used to estimate statistical distributions of bottled and tap water $C_{EXP,i}$ for each considered compound, according to the procedure explained in section S1.1. Since no pair-wise correlations were found among the considered compounds' concentrations, they were sampled and combined as independent variables. A high percentage of C_{EXP} data was lower than the analytical limit of quantification (LOQ). Hence, statistical distributions were fitted to data which include left-censored data by adopting the Maximum Likelihood Estimation method for left-censored data (MLE_{LC}) explained in Cantoni et al. (2020). From each compound-related $C_{EXP,i}$ statistical distribution, 1,000 values were sampled independently, and then combined by the use of Eq. (1) to obtain 1,000 values of the cumulative exposure mixture concentration, C_{MIX}, which includes all the considered contaminants contributions. This procedure has been performed for four different C_{MIX}, namely bottled and tap water C_{MIX} for alkylphenol and phthalate groups of compounds.

2.1.2.2. WIRs data collection. Once bottled and tap water C_{MIX} were defined, they were multiplied by WIR [L kg^{-1} day^{-1}], which is the ratio between daily water consumption and average body weight, to derive the mixture equivalent dose, $Dose_{MIX}$ [mg kg^{-1} day^{-1}], following Eq. (5):

$$Dose_{MIX} = C_{MIX} \times WIR \quad (5)$$

$Dose_{MIX}$ statistical distributions for both alkylphenols and phthalates were then estimated according to the procedure explained in section S1.1.

Average body weight was considered constant and equal to 60 kg (Baken et al., 2018). As for the daily water consumption, two scenarios were investigated: (i) it was set as a constant value, equal to 2 L day^{-1} (Baken et al., 2018), or (ii) it was estimated from real water consumption data collected from literature concerning different countries worldwide. Among those countries for which alkylphenols or phthalates C_{EXP} data were available, only countries with sufficient water consumption data collected through robust surveys were selected. For these countries, data about total daily water consumption and how it is split between bottled and tap water were collected. The list of countries considered for water consumption data collection, with a statistical summary recap, is reported in Table S13, while the number of available data for the consumption of total, bottled and tap water with their associated statistical summary data and references, are reported in Table 1. Since the collected literature data regarding the water intake variability in people of different ages were not reliable enough, this aspect was not considered for the risk estimation.

Lastly, the considered countries have been divided in different clusters associated to DW consumers' habits. The cluster analysis has been performed dividing countries into three clusters: the appropriate clusters number was defined based on shape and scale of the points distribution in the available dataset, which is constituted by two variables: total water consumption and fraction of bottled water consumption. An extension of the k-means clustering algorithm, namely COD-means algorithm (Constrained Outlier Detection) was applied. Specifically, a constraint which ensures that all data from the same country must be included into the same cluster has been imposed, similar to the approach described by Imran et al. (2017). For each cluster, raw data coming from each country were merged and the statistical distributions for total and bottled water consumption were estimated to be then used in the case study explained in paragraph 2.2.

2.1.3. Risk characterization

For the risk characterization step, 1,000 data points were sampled from the statistical distributions obtained for $DWTL_{REF}$ and for the alkylphenol and phthalate $Dose_{MIX}$, both for bottled and tap water. From the sampled data sets, the corresponding series of 1,000 BQ_{MIX} values were computed as:

$$BQ_{MIX} = \frac{Dose_{MIX}}{DWTL_{REF}} \quad (6)$$

These values were used to estimate BQ_{MIX} statistical distributions for the four combinations of contaminant and DW type (see section S1.1), which were employed to extrapolate three different data: (i) the maximum probabilistic BQ_{MIX} ($BQ_{PROB,MAX}$), corresponding to the 99th percentile of the fitted BQ_{MIX} distribution; (ii) the probability of BQ_{MIX}, where BQ_{MIX} is larger or equal to 1 ($P(BQ_{MIX} > 1)$), and (iii) BQ_{MIX}>0.1 ($P(BQ_{MIX} > 0.1)$), both resulting from BQ_{MIX} estimation uncertainties. $P(BQ_{MIX} > 1)$ and $P(BQ_{MIX} > 0.1)$ represent the percentage of the total area underlying the BQ_{MIX} probability density curve that is above the

Table 1
Input parameters for C_{EXP} and DW consumption (DWC), as a function of water type (bottled, BOT, and tap, TAP): number of available data and references, range and mean.

Input group	Input parameter	DW type	# available data	# available references	Range	Mean	Unit
ALKYLPHENOLS	$C_{EXP,\ BPA}$	BOT	57	5	0.0008 – 1.2	0.10	µg L^{-1}
		TAP	104	26	0.0005 – 0.4	0. 06	µg L^{-1}
	$C_{EXP,\ NP}$	BOT	42	11	0.0175 – 0.5	0.18	µg L^{-1}
		TAP	108	21	0.0016 – 1.3	0.24	µg L^{-1}
	$C_{EXP,\ OP}$	BOT	20	9	0.0011 – 0.5	0.08	µg L^{-1}
		TAP	72	11	0.0004 – 1.1	0. 0	µg L^{-1}
PHTHALATES	$C_{EXP,\ DEHP}$	BOT	69	26	0.017 – 24.4	3.16	µg L^{-1}
		TAP	49	23	0.0097 – 25	1.49	µg L^{-1}
	$C_{EXP,\ DBP}$	BOT	88	32	0.049 – 85.6	10.67	µg L^{-1}
		TAP	51	25	0.0013 – 9.3	0.78	µg L^{-1}
	$C_{EXP,\ BBP}$	BOT	25	17	0.002 – 2.3	0.52	µg L^{-1}
		TAP	33	17	0.0014 – 0.9	0.10	µg L^{-1}
	$C_{EXP,\ DiBP}$	BOT	31	7	0.026 – 2.5	0.34	µg L^{-1}
		TAP	21	8	0.0148 – 1.3	0.19	µg L^{-1}
WIR	DWC	BOT			0.05 – 0.73	0.35	L day^{-1}
		TAP	41	24	0.20 – 1.62	0.75	L day^{-1}
		TOT			0.42 – 1.89	1.10	L day^{-1}

BQ_{MIX} value of respectively 1 and 0.1.

2.2. $QCRA_{MIX}$ application for scenarios comparison

The $QCRA_{MIX}$ procedure has been applied to three scenarios, differing for the type of DW source and WIR values.

In the first two, the risk deriving from consumption of bottled water (scenario 1 - BOT) or tap water (scenario 2 - TAP), due to the occurrence of alkylphenols or phthalates, is compared. In this case study, it has been assumed that daily water consumption is totally based on bottled or tap water, and it is constant and equal to 2 L day^{-1}, which, divided by average body weight (60 kg), results in a fixed WIR equal to 0.033 L kg^{-1} day^{-1}, standard value used for defining DW regulation limits (Baken et al., 2018). In the third scenario, actual data on total water consumption and fractions of bottled and tap water for three different clusters of countries were considered, with their associated uncertainties (see paragraph 2.1.2.2). Differently from the first two scenarios, in the $QCRA_{MIX}$ procedure applied to each cluster of countries, the statistical distributions of both total water consumption and fraction of bottled water on the total were included. Hence, health risk deriving from the three realistic DW consumption clusters were evaluated, describing the most common consumers' habits.

Furthermore, an ANOVA was performed to assess whether the country was a significant factor in defining alkylphenols and phthalates concentrations in DW. The p-value exceeded 0.05, which indicates that the differentiation of the concentration dataset for the clusters identified in the third scenario was not necessary. Therefore, it is justifiable to use the same dataset of worldwide concentrations for all clusters.

3. Results and discussion

3.1. Hazard assessment

The obtained RPF values and $DWTL_{REF}$ statistical distributions are shown for alkylphenols and phthalates. This step of the $QCRA_{MIX}$ procedure was kept the same for all the analysed scenarios, being the toxicological characterization dependent only on the considered compounds.

3.1.1. RPFs definition

Results for BPA and NP dose–response curves, fitted with the exponential model, are presented in Fig. S1 and Fig. S2 and described in detail in section S2. Generally, male rats appeared to be more sensitive compared to females to kidney weight increase induced by BPA and NP at lower doses, thus males were the selected sex for the RPF extrapolation. Among the generations, the F1 generation showed a lower BPA BMD_{10} (309.3 mg kg^{-1} day^{-1}) compared to F0 (352.4 mg kg^{-1} day^{-1}) which implies that F1 is the most sensitive generation (Fig. S2). Moreover, male F1 was also selected by EFSA as the most sensitive subgroup for BPA PoD estimation. Hence, F1 male dose–response data were chosen to derive NP's RPF of 3.0. Since Bayer (1982) is a confidential study, the dose–response data of OP are not available. ECHA reported a OP NOAEL of 22.5 mg kg^{-1} day^{-1}, which is comparable with NP's NOAEL reported by Tyl et al. (2006) (15 mg kg^{-1} day^{-1}). Hence, even if NOAELs are not equipotent doses, since the effect size is unknown at the NOAEL level, it was assumed that OP and NP have a similar potency and, consequently, the same RPFs of 3.0 is assumed. In general, it can be concluded that NP and OP are more potent than BPA with respect to effects on relative kidney weight.

Regarding phthalates, the adopted RPFs were estimated by EFSA (2019). RPFs for BBP and DBP were 0.1 and 5, respectively. DiBP was not considered in the EFSA report, but it was reported to have comparable reproductive toxicity dose–response data with respect to DEHP. Hannas et al. (2011) evaluated the testosterone production dose–response curves of DiBP and DEHP on F1 male rats with oral exposure of 1 week, and, since the two compounds' dose–response curves overlapped, DiBP and DEHP were assumed to be equally potent, thus, a RPF of 1 was assumed for DiBP.

3.1.2. $DWTL_{REF}$ distributions estimation

For BPA, the input data and the DWTL distribution were obtained as described in Cantoni et al. (2021b); in detail, the DWTL distribution is $\mathrm{lognorm}(2.48; 1.69)$, plotted in Fig. S3.

For DEHP, the APROBA-Plus tool provides an approximate probabilistic DWTL (8.598 μg kg^{-1} day^{-1}), defined as the 5th percentile of the DWTL distribution, which aims to protect 99% of the population against testis effects. Thus, the output DWTL is the dose below which 99% of the population is protected against critical effects for small reproductive organs and testis atrophy. In addition, the APROBA-Plus tool was used to include all the hazard assessment uncertainties and estimate the statistical distribution of the probabilistic DWTL, that was found to be well described by a lognormal distribution $\mathrm{lognorm}(4.60; 1.49)$, plotted in Fig. S4. These results show that, if a deterministic CRA approach would have been used, the deterministic DWTL obtained would have been equal to 10 μg kg^{-1} day^{-1}, derived by applying a 20% allocation factor to the EFSA's HBGV for DEHP (50 μg kg^{-1} day^{-1}), which is higher than the obtained approximate probabilistic DWTL. The deterministic DWTL corresponds to the 6.1% percentile of the probabilistic DWTL distribution (Fig. S4). In addition, an uncertainty analysis provided by the APROBA-Plus tool allowed to highlight which of the AFs display the main contributions to the overall DWTL uncertainty (see Tab. S10). The largest contributor to DWTL uncertainty is the AF accounting for the NOAEL-to-BMD conversion, with 43% contribution, followed by the intraspecies factor (36% contribution), the interspecies factor (20%) and the interspecies scaling (1%). Therefore, by considering the scarcity of available toxicological data present for this class of contaminants, a stochastic approach is highly recommended, to properly address the related uncertainties in the evaluation and quantify their contribution to the final output of the risk analysis.

3.2. Exposure assessment and risk characterization applied to scenarios

The obtained $Dose_{MIX}$ and BQ_{MIX} statistical distributions are here reported for the three investigated scenarios. In the exposure assessment and risk characterization steps, results are directly linked to the scenarios assumptions, being then strongly dependent on water consumption, both in terms of type of source water (fraction of bottled or tap water consumption) and overall consumed quantity (total water consumption).

3.2.1. Bottled and tap water comparative $QCRA_{MIX}$

Firstly, $QCRA_{MIX}$ was applied to two scenarios: scenario 1, indicated as BOT, and scenario 2, indicated as TAP, in which water consumption (equal to 0.033 L kg^{-1} day^{-1}) is assumed to be totally based on, respectively, bottled water and tap water. In this way, the application of $QCRA_{MIX}$ permits to compare bottled and tap water in terms of health risk associated to the presence of alkylphenols or phthalates.

The estimated statistical distributions of the BQ_{MIX} for alkylphenols and phthalates in the two scenarios are shown in Fig. 2. In Table 2 the statistical distributions and the associated parameters are reported for $Dose_{MIX}$ and BQ_{MIX}, together with the three outputs obtained from the risk characterization: $BQ_{PROB,MAX}$, $P(BQ_{MIX} > 1)$ and $P(BQ_{MIX} > 0.1)$, as defined in section 2.1.3.

The obtained results show a very diversified picture, depending on the aspect that is evaluated for the comparison. The application of the $QCRA_{MIX}$ highlights that the consumption of both tap and bottled water results to be a potential health risk determinant for either alkylphenols and phthalates, having $BQ_{PROB,MAX}$ values higher than 1 and a probability of BQ_{MIX} exceeding the threshold value of 1, ranging from 0.06 % to 1.44 %, depending on the compounds and the water source. In contrast to deterministic CRA approachs (Riva et al., 2018; Liu et al., 2015) concluding negligible health risks (HI lower than 1), the $QCRA_{MIX}$

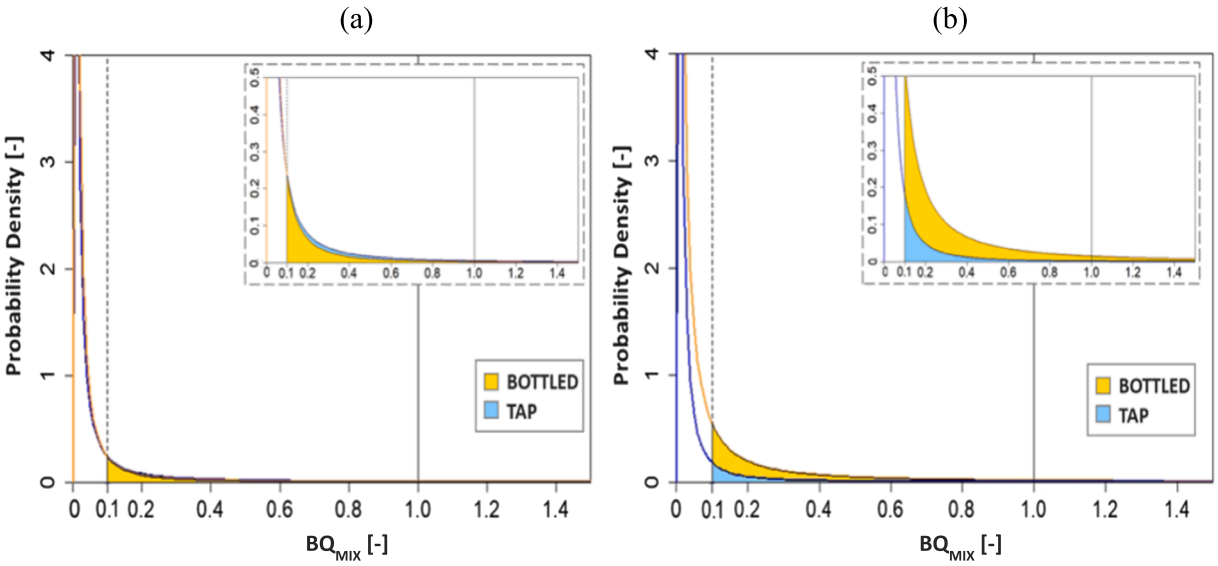

Fig. 2. BQ_{MIX} probability density of bottled and tap water for: (a) alkylphenols (b) phthalates. The inset in each figure represents a zoom of the main graph.

Table 2
Statistical distributions of probabilistic $Dose_{MIX}$ and BQ_{MIX} (distribution parameters reported in brackets), maximum quantitative BQ and probability of quantitative BQ exceeding the threshold values of 0.1 and 1 for the three scenarios.

	Scenario	$Dose_{MIX}$ [μg/L]	BQ_{MIX} [-]	$BQ_{PROB,MAX}$ [-]	$P(BQ_{MIX} > 0.1)$ [%]	$P(BQ_{MIX} > 1)$ [%]
1	**BOT-ALK**	Weibull(0.927, 0.019)	lognorm(-6.949, 2.337)	1.67	1.49	0.06
	BOT-PHTH	lognorm(-1.806, 2.317)	lognorm(-6.291, 2.879)	2.85	8.30	1.44
2	**TAP-ALK**	Weibull(0.526, 0.011)	lognorm(-7.940, 3.058)	1.49	3.26	0.47
	TAP-PHTH	lognorm(-2.886, 1.490)	lognorm(-7.371, 2.310)	1.39	1.41	0.07
3	**Cluster1-ALK**	lognorm(-5.110, 1.366)	lognorm(-7.512, 2.367)	1.32	1.39	0.075
	Cluster1-PHTH	lognorm(-2.366, 1.456)	lognorm(-6.991, 2.261)	1.76	1.90	0.10
	Cluster2-ALK	lognorm(-5.100, 1.081)	lognorm(-7.501, 2.154)	1.08	0.79	0.025
	Cluster2-PHTH	lognorm(-2.282, 1.732)	lognorm(-6.906, 2.472)	2.05	3.13	0.26
	Cluster3-ALK	lognorm(-5.469, 1.181)	lognorm(-7.870, 2.240)	0.87	0.65	0.022
	Cluster3-PHTH	lognorm(-2.682, 1.625)	lognorm(-7.306, 2.390)	1.54	1.82	0.11

procedure offers more insights in the accuracy and reliability of the risk estimation, by yielding the whole uncertainty distribution of BQ_{MIX}.

Comparing bottled and tap water based on the BQ_{MIX} distribution curve (see Fig. 2), it can be noted that for alkylphenols tap water is responsible for a slightly higher BQ_{MIX} distribution curve. For phthalates, bottled water clearly shows a higher risk.

When the goal is a quantitative comparison of the generated health risks, it is crucial to evaluate which of the three risk characterization outputs, namely $BQ_{PROB,MAX}$, $P(BQ_{MIX} > 0.1)$ and $P(BQ_{MIX} > 1)$, is the most appropriate to consider. In fact, as evident from Table 2, the comparison is deeply affected by the considered outputs, which are related to different features of the human health risk. $BQ_{PROB,MAX}$ is more appropriate when acute effects on human health are analysed, describing the most critical situation that could happen, even with low probability. When a chronic effect is evaluated, as it can be the case for the presence of chemicals in DW, $P(BQ_{MIX} > 1)$ and $P(BQ_{MIX} > 0.1)$ are the most appropriate parameters, indicating the probability of BQ_{MIX} exceeding threshold values and, thus, 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 ($BQ_{MIX} > 0.1$). If $P(BQ_{MIX} > 0.1)$ is evaluated as comparison parameter, alkylphenols show a $P(BQ_{MIX} > 0.1)$ for tap water that is twice the one for bottled water (see Tab. 2), while phthalates show a $P(BQ_{MIX} > 0.1)$ for bottled water which is almost six times the tap water one. Secondly, if a comparison between alkylphenols and phthalates is made considering the same type of water, for bottled water, the $BQ_{MIX,PHTH}$ is definitely higher than the $BQ_{MIX,ALK}$, with a $P(BQ_{MIX} > 0.1)$ equal respectively to 8.30 and 1.49. For tap water, alkylphenols $P(BQ_{MIX} > 0.1)$ is twice the phthalates one.

It can be concluded that in bottled water, although the health risk due to alkylphenols is not negligible, the risk due to phthalates presence is significantly higher. In tap water the health risks of the two groups of compounds are in the same order of magnitude, but the major risk is more related to alkylphenols. Alkylphenols, mainly BPA and NP, occur in tap water because of its prolonged contact with many different pipe materials in the distribution system (Rajasärkkä et al., 2016). In bottled water, even if both groups of compounds are detected, many studies reported higher presence of phthalates residues. This can be attributed to: (i) water contamination in the bottling plant and (ii) migration of plasticizers from the bottle material to the water, as confirmed by the increase in their concentration with storage time and temperature (Luo et al., 2018).

The $QCRA_{MIX}$ application allowed to highlight that the highest potential risk is related to the presence of phthalates in bottled water, having the maximum values for $BQ_{PROB,MAX}$, that is almost twice the others, $P(BQ_{MIX} > 0.1)$, that is almost three times the others, and $P(BQ_{MIX} > 1)$, that is one order of magnitude greater than the others. Given this result, it would be relevant to extend the $QCRA_{MIX}$ application to evaluate the effect of DW bottles storage on the health risk, depending on storage conditions. Finally, when the $QCRA_{MIX}$ procedure is applied to compare the risks related to the consumption of water containing alkylphenols or phthalates, it must be considered that the related health

effects are totally different: the endpoint critically affected by alkylphenols is kidney weight, while it is the male reproductive system for phthalates. Thus, besides the two groups of compounds show similar BQ_{MIX} values, the adverse effects are not directly comparable and a further development of the $QCRA_{MIX}$ procedure would be necessary.

To highlight the importance of the toxicological aspect, in Fig. 3, the distributions of C_{EXP} data collected from literature and the percentage contribution that each single compound has on the overall resulting BQ_{MIX} are reported, for both groups of compounds, differentiated per bottled and tap water.

For alkylphenols, the compound that is present with higher concentrations in both bottled and tap water is NP, followed by BPA. For phthalates, the situation is slightly different in the two types of DW. In bottled water DBP is present with the highest concentrations, followed by DEHP. In tap water, DBP and DEHP have similar concentrations, slightly higher than DiBP and BBP. Comparing the compounds' C_{EXP} distributions, with their associated percentage contribution to the BQ_{MIX}, it can be observed that the C_{EXP} distribution is well reflected in the BQ_{MIX} contribution, when a compound has a significantly higher C_{EXP} compared to the others. However, in case of similar C_{EXP} distributions, variations in the compounds ranking can be observed in BQ_{MIX} percentage contributions with respect to C_{EXP} distributions, due to the influence of the RPF factors, which are proxy variables of the compounds' toxicological characterization. In particular, for alkylphenols, it can be seen that OP, with negligible concentrations compared to BPA but RPF equal to 3, has a contribution to $BQ_{MIX,ALK}$ that is directly comparable with the one of BPA. As for phthalates, focusing on tap water, it can be seen that the four C_{EXP} distributions are very similar, but the DBP's contribution to $BQ_{MIX,PHTH}$ is notably higher compared to the others, due to its RPF, equal to 5. Hence, including the toxicological characterization aspect, expressed in terms of RPFs, is fundamental to assign the proper weight that each compound has on the health risk of a mixture, since contaminants' concentrations in DW are not sufficient to predict the contributions to the health risk. This evidence has important implications highlighting that the analysis of concentration data is insufficient to assess risks, but instead a full risk-based approach is recommended for, among others: (i) decision makers which aim to evaluate compounds to be prioritized in DW regulations, (ii) water utility managers for ranking of compounds targeted for treatments optimization, and (iii) the scientific community to understand which compounds are more interesting to be measured, for which of them better analytical methods should be defined and new research studies should be performed to understand the main sources of contamination. In this case, NP for alkylphenols and DBP for phthalates were the compounds with both the highest concentration in DW and the most severe health effects (i.e., highest RPF), thus, they were the most relevant compounds for the BQ_{MIX} determination, followed respectively by BPA and DEHP.

3.2.2. *Drinking water consumers' behaviour-based scenarios*

In the third scenario, it has been evaluated how DW consumption habits affect the health risk by considering actual data on total water consumption and fractions of bottled and tap water, derived from DW consumption in different countries worldwide.

3.2.2.1. Consumers' behaviour cluster analysis. The total and bottled water consumption country-related data collected from literature for 13 countries are shown in Fig. S5. From this dataset, three clusters of countries were identified, representative of different DW consumption behaviours, in terms of total water consumption and preferred DW source between bottled and tap water. In Table S13, it is indicated to which cluster each country has been assigned. The identified clusters

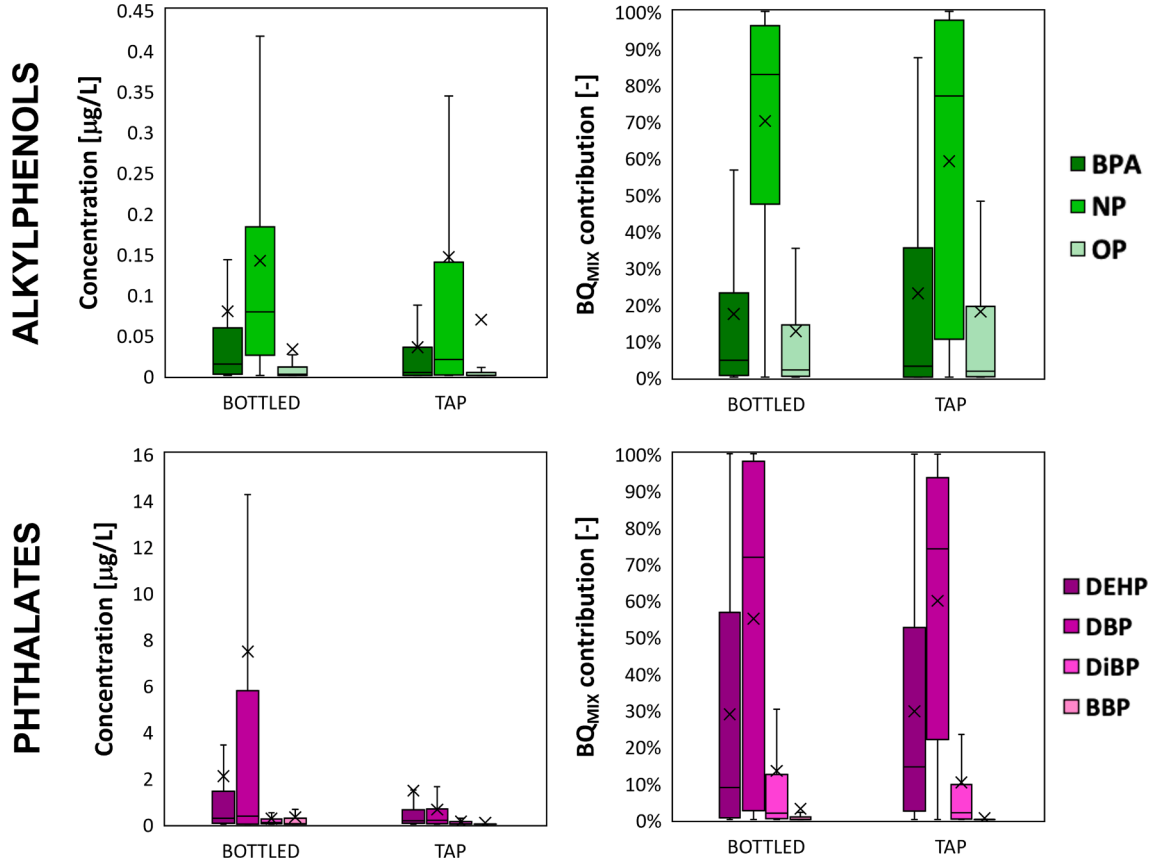

Fig. 3. Alkylphenols and phthalates concentration (column a) and percentage contribution to the BQ_{MIX} (column b), differentiated per compounds' group and type of DW.

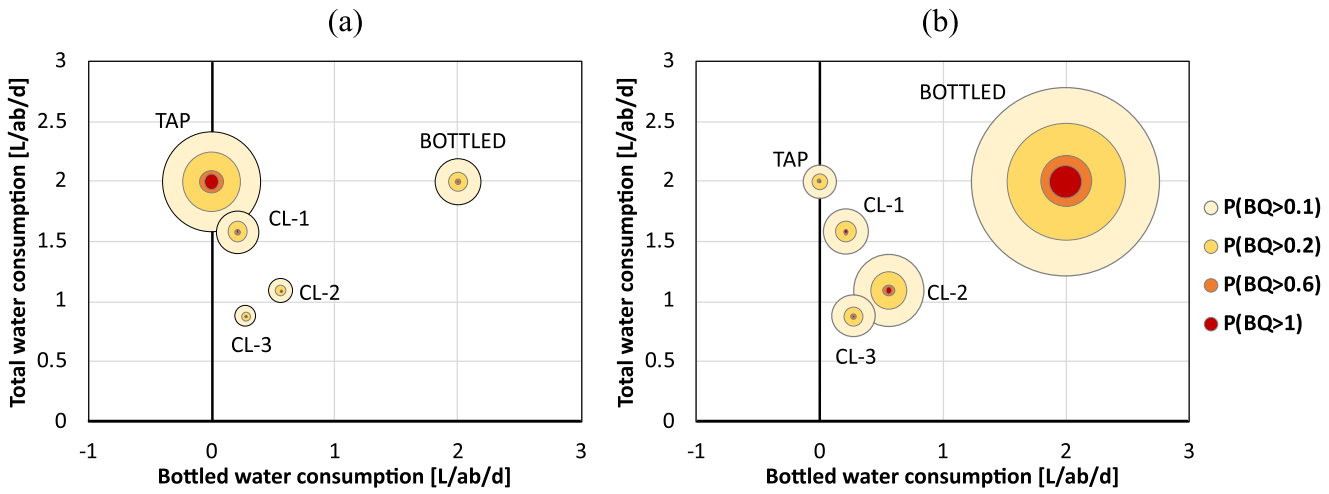

Fig. 4. Bubble charts with bubble centres located according to the different scenarios of water consumption habits. Bubble areas/diameters are proportional to the probability of BQ_{MIX} exceeding different risk thresholds for: a) alkylphenols, and b) phthalates. Total water consumption is intended as the sum of bottled and tap water.

highlight three different DW consumption habits: (i) cluster 1 (CL-1) contains countries with high values of total water consumption (around 1.5 L day^{-1}) and a prevalence of tap water consumed (from 77 % to 97 % with median of 86 % of tap water on the total consumption), (ii) cluster 2 (CL-2) includes those countries with lower values of total water consumed (around 1.0 L day^{-1}) and an almost equal fraction of bottled and tap water consumed (from 25 % to 64 % with median of 54 % of tap water on the total consumption), (iii) cluster 3 (CL-3) contains countries with total water consumption values similar the CL-2 ones (around 1.0 L day^{-1}), but with a higher prevalence of tap water consumed (from 36 % to 91 % with median of 68 % of tap water on the total consumption).

3.2.2.2. Effect of drinking behaviour on human health risk. The results obtained for the third scenario are graphically visualized in Fig. 4, together with first and second scenarios. For the third scenario, BQ_{MIX} and $Dose_{MIX}$ statistical distributions with their associated parameters are reported in Table 2, together with the three different outputs obtained from the risk characterization.

In Fig. 4 each bubble corresponds to a specific case of the simulated scenarios, thus, there are two bubbles for scenarios 1 and 2, and three bubbles for the third scenario, related to the three identified clusters. Each bubble centre is located according to its mean values of total water consumption, reported in the y-axis, and bottled water consumption, reported in the x-axis, while tap water consumption can be obtained by subtracting bottled water consumption from total water consumption. For example, for the first two scenarios, total water consumption is assumed equal to 2 L day-1, so both bubbles have y-coordinate equal to 2. However, in scenario 1 (BOT) all the consumed DW is bottled water, thus, it is equal to the total water consumption value (2 L day-1) and the bubble is located at the x-coordinate corresponding to 2, while for scenario 2 (TAP), DW consumption is exclusively based on tap water, with no bottled water consumption (0 L day-1), thus the bubble is located at the x-coordinate corresponding to 0. Each bubble diameter is proportional to the probability of BQ_{MIX} exceeding four health risk threshold values (i.e. 0.1, 0.2, 0.6 and 1), where the first three values can be used as quantitative early-warning risk values, while the threshold equal to 1 identifies the presence of a risk. The first evidence is that the three clusters, based on actual DW consumption data, showed a total water consumption (y-coordinate) that is lower than the 2 L day^{-1} usually used in risk assessments. In particular, by estimating the probability distribution of all available data on total water consumption in all the countries, it was found that 2 L day^{-1} corresponds to the 98.0 percentile of the distribution. Therefore, it is interesting to evaluate whether 2 L day^{-1}, being a precautionary high value, is actually realistic.

The results for the actual DW consumption data (the three clusters) are quite different for the two groups of compounds. For alkylphenols, either $P(BQ_{MIX} > 0.1)$, $P(BQ_{MIX} > 1)$ (Tab. 2) and the bubbles' sizes (Fig. 4), CL-1 shows higher risk compared to the others that have similar values (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 (tap or bottled). This is confirmed by the regression analysis evaluating the influence of total water consumption and bottled water consumption percentage on $P(BQ_{MIX} > 0.1)$, whose results are reported in Table S14. For alkylphenols only the total water consumption factor had a significant influence on $P(BQ_{MIX} > 0.1)$, with a p-value 0.016 lower than the significance level ($\alpha = 0.05$); the bottled water consumption percentage was found not to have a significant influence (p-value = 0.083). On the contrary, for phthalates, bottled water consumption shows significant higher $P(BQ_{MIX} > 0.1)$ and $P(BQ_{MIX} > 1)$ compared to tap water consumption, according to the regression results for phthalates (Tab. S14). It emerges that both the total DW consumption and the percentage of bottled water consumption had significant influence on phthalates $P(BQ_{MIX} > 0.1)$ (p-values lower than 0.05), but the percentage of bottled water consumption showed higher standardized effect (18.87) compared to total water consumption (6.58). This finding highlights that the type of DW consumed is more relevant with respect to quantity of water consumed in influencing the final risk due to phthalates. In fact, CL-2, which is the cluster with the highest fraction of bottled water consumed, presents $P(BQ_{MIX} > 0.1)$ and $P(BQ_{MIX} > 1)$ respectively equal to 3.13 and 0.26, which are at least twice the values estimated for water consumption based exclusively on tap water, equal to 1.41 and 0.071, even if it has a total water consumption that is almost twice the one of CL-2. In addition, also CL-1 and CL-2 show higher values of $P(BQ_{MIX} > 0.1)$ and $P(BQ_{MIX} > 1)$ compared to scenario 2 (tap water), since they include a small portion of bottled water consumed. These findings point out that considering the actual water consumption data, both in terms of total DW consumption and on the type of DW, could lead to a different and more realistic risk estimation, and that this is an essential aspect to consider for a more accurate risk assessment.

4. Conclusions

In the present work, a new procedure for probabilistic risk assessment, is proposed in order to estimate and compare the health risk due

to mixtures of compounds in DW sources. This assessment, referred to as QCRA, takes the endpoints which are affected by chronic effects, into account. The risk due to the presence of alkylphenols or phthalates in DW has been quantitatively evaluated for a case study where bottled and tap water are involved, and in which the uncertainties in either exposure and hazard assessment steps are taken into account. Among these uncertainties, which are inevitably associated to CECs, data gaps and source data quality, particularly associated with CECs concentrations detection and reliability of their toxicological studies, represent the main barriers to the application of this procedure to other groups of compounds.

It emerges that the consumption of both bottled and tap water implies a potential health risk either for alkylphenols and phthalates. In particular, the health risk when consuming bottled water is mainly due to the presence of phthalates, while for tap water, alkylphenols are the most relevant compounds for risk determination. Nevertheless, it must be reminded that these two groups of compounds, from the toxicological point of view, are different since they act on different critical endpoints: alkylphenols are responsible for changes in kidneys weight, while phthalates affect male reproductive system. Hence, further research is needed to aggregate the risks of these two separate groups and their corresponding endpoints in order to draw conclusions on which of the two DW sources is the most critical mixture. In addition, a full risk-based approach could be useful either for decision makers and the scientific community for the prioritization of compounds in, respectively, DW regulations and research. Finally, the analysis of actual DW consumption data pointed out that adopting actual consumption data leads to more realistic risk estimation which can aid in understanding how consumers' behaviour affect health risks.

CRediT authorship contribution statement

Luca Penserini: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Beatrice Cantoni:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Dirk Vries:** Validation, Writing – review & editing. **Andrea Turolla:** Validation, Writing – review & editing. **Patrick W.M.H. Smeets:** Validation, Writing – review & editing. **Bas G.H. Bokkers:** Methodology, Validation, Writing – review & editing. **Manuela Antonelli:** Supervision, Conceptualization, Writing – review & editing, Funding acquisition.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2022.107294.

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