



# Chemical migration from reusable plastic bottles: Silicone, polyethylene, and polypropylene show highest hazard potential in LC-HRMS analysis

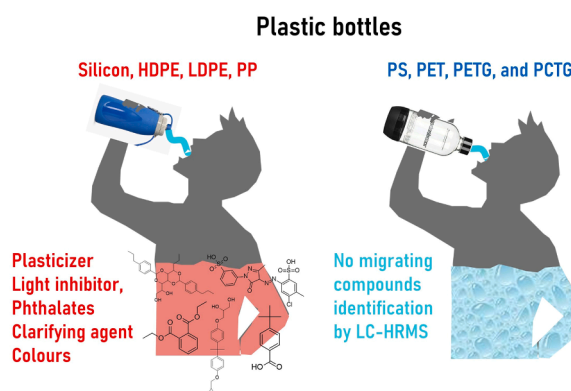
Selina Tisler<sup>\*</sup>, Nastacha Kristiansen, Jan H. Christensen

Analytical Chemistry Group, Department of Plant and Environmental Science, University of Copenhagen, Thorvaldsensvej 40, Frederiksberg C 1871, Denmark

## HIGHLIGHTS

- Every bottle type released a unique chemical fingerprint into the water.
- Highest number of chemicals migrated from Silicone, HDPE, LDPE, and PP.
- Lowest number of chemicals migrated from PS, PET, PETG, and PCTG.
- Silicone bottles leached concerning phthalates and plasticizers into water.
- PP bottles showed migration of light inhibitors, clarifier and coating agents.

## GRAPHICAL ABSTRACT



## ARTICLE INFO

### Keywords:

Non-target screening  
Drinking water  
Food contact materials  
Non-intentionally added substances  
Phthalates  
Bisphenol  
Clarifying agents

## ABSTRACT

Estimating the chemical hazards of drinking water stored in reusable plastic bottles is challenging due to the numerous intentionally and unintentionally added chemicals. To address this, we developed a broad screening strategy using evaporation enrichment and liquid chromatography high-resolution mass spectrometry (LC-HRMS) to evaluate migration of non-volatile chemicals from various reusable plastic bottles. The study analyzed a wide range of materials, revealing significant variability in chemical profiles across different bottle types. Over 70 % of nearly 1000 unknown compounds were unique to specific bottles. Silicone, HDPE, LDPE, and PP bottles showed the highest migration rates, with silicone releasing the most unknowns, but also phthalates and plasticizers. PP bottles exhibited concerning migration of clarifying agents and bisphenol A derivatives. In contrast, PS, PET, PETG, and PCTG had minimal migration, indicating lower health risks. These findings highlight the need for comprehensive assessments of plastic materials to improve consumer safety.

## 1. Introduction

The global demand for reusable food packaging has increased,

supporting the efficient use of natural resources [1]. In particular, the market for reusable plastic beverage containers has grown, providing products that are more durable for everyday use [2]. This has resulted in

<sup>\*</sup> Corresponding author.

E-mail address: [seti@plen.ku.dk](mailto:seti@plen.ku.dk) (S. Tisler).

<https://doi.org/10.1016/j.jhazmat.2024.136391>

Received 29 August 2024; Received in revised form 21 October 2024; Accepted 1 November 2024

Available online 12 November 2024

0304-3894/© 2024 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

a wide variety of plastic materials, as food contact materials (FCMs) are produced from different monomers and co-monomers, which serve as essential building blocks [3]. These monomers undergo chemical processes involving the addition of various intentionally added substances (IAS) to form polymers. Chemicals can migrate not only from the polymers themselves but also from packaging components, such as inks, sealants, and coatings, contributing to the complexity of substances migrating into food. Common classes of substances detected in food include polymer additives such as plasticizers, slip agents, stabilizers, antioxidants, unreacted monomers, and processing agents. Thus, FCMs can have a high chemical complexity, with more than 12000 IAS and an even higher number of previously uncharacterized, non-intentionally added substances (NIAS) [4]. NIAS can be impurities introduced during production and can also be breakdown or transformation products (TPs) formed during the use of FCMs by stressors such as temperatures or physical degradation. Most FCMs on the market fail to meet the European Food Safety Authority (EFSA) safety requirements because comprehensive risk assessments for all migrating substances are not feasible with current target analysis methods [5,6,4,7-9]. Given the complexity of the materials, it is essential to apply broad screening methods. Besides the analytical platform, the comprehensiveness of the analysis also relies heavily on sample preparation, which plays a key role in determining the chemicals detected in the final results. Using drinking water as a medium, rather than food simulants, has been shown to closely replicate real-world bottle usage while effectively detecting a broad range of migrating IAS and NIAS [10]. However, enrichment strategies are required due to the low concentrations of migrating compounds. Solid-phase extraction (SPE) is commonly used for water enrichment, but it may introduce plasticizer background contamination [11] in the analysis of FCMs. Vacuum evaporation concentration (VEC) has proven to be a promising alternative, effectively capturing even more polar compounds suspected of migrating into water [12]. This study aimed to develop a comprehensive strategy for evaluating the chemical migration from various reusable plastic bottles, utilizing VEC enrichment combined with liquid chromatography (LC) high resolution mass spectrometry (HRMS) analysis. This was done by creating chemical fingerprints, revealing the unique combination of known and unknown compounds migrating from the individual materials. The objective was to investigate a wide range of materials from different manufacturers to identify those with higher and lower chemical migration rates. The findings aim to enhance consumer safety and guide future material selection.

## 2. Material and methods

### 2.1. Chemicals

The analytical standards, with purities ranging from 95 % to 99.5 %, consisted of chemicals previously identified as migrating from FCMs. The available standards included tributyl O-acetylcitrate, quinacridone, 2,4-di-tert-butylphenol, 2-phenoxyethanol, 3,5-di-tert-butyl-4-hydroxybenzaldehyde, 3,5-di-tert-butyl-4-hydroxybenzyl alcohol (Ionox 100), 4-dodecylbenzenesulfonic acid, 4-ethylphenol (4-EP), 4-methylumbelliferon, 4-nonylphenol, 4-tert-butylphenol, benzophenone, bis(2-ethylhexyl)phthalate, dibutyl maleate, dibutyl phthalate, diethyl phthalate (DEP), diethyl-m-toluamide (DEET), dimethyl phthalate, erucamide, octabenzene, tributyl citrate, tributyl phosphate, triclocarban, and tris(2-butoxyethyl) phosphate. The solvents used for sample preparation and the analytical method are detailed in Section S2.1.

### 2.2. Selection of reusable plastic bottles

In total 16 different types of reusable bottles were investigated, varying by plastic type and country of origin (Table 1). Pictures and brand of the bottles are shown in Table S1 and Fig. S1. The plastic types included polyethylene terephthalate (PET), high-density polyethylene

**Table 1**

Reusable bottles investigated in this study.

Sample	Plastic type	Color	Country of origin
HDPE yellow	HDPE	yellow	Sweden
HDPE blue	HDPE	blue	New Zealand
LDPE pink 1	LDPE	pink	India
PP purple	PP	purple	New Zealand
PP clear	PP	clear	China
PP pink	PP	pink	Thailand
Silicone blue	Silicone	blue	China
Ecozen salmon	ECOZEN	salmon	China
PP black	PP	black	Sweden
PET clear	PET	clear	Israel
LDPE pink 2	LDPE	pink	China
PS clear	PS	clear	China
PCTG clear	PCTG	clear	China
PETG grey	PETG	grey	China
Tritan blue	Tritan™	blue	New Zealand
Tritan clear	Tritan™	clear	China

(HDPE), low-density polyethylene (LDPE), polypropylene (PP), polystyrene (PS), polycyclohexylenedimethylene terephthalate glycol-modified (PCTG), polyethylene terephthalate glycol-modified (PETG), tritan (a BPA-free copolyester), ecozen (a bio-based copolyester) and silicone. The bottles were manufactured in Israel, Sweden, New Zealand, Netherlands, Thailand, China, and India. Each type was tested in triplicate. Before preparation, bottles were stored dry at room temperature. All bottles were unused and purchased in Denmark or Sweden within the same year of investigation. For blank controls, 250 mL laboratory Duran wide neck glass bottles were washed and heated in a kiln oven at 550 °C for 4 h to remove contaminants.

### 2.3. Migration experiments

For all experiments, we used tap water that meets drinking water quality standards and is safe for consumption. Before the migration experiment, all reusable plastic and control bottles were washed by filling them with tap water that had run for 10 min and then emptying the water from the bottles. The samples were prepared in eight batches, each following the same procedure. Each batch included up to three types of bottles (prepared in triplicate) and at least two blanks. In each batch, tap water was equally distributed among the bottles, filling them to 90 % of their capacity (volume varied from 400 to 2000 mL). The bottles were not completely filled to avoid contact with the lids, which were not part of the study. They were stored vertically and undisturbed in the dark at room temperature (approximately 21 °C) for 48 h. The migration time was aligned with a previous study at 24 h [10] to account for the lower enrichment factor employed in this investigation. Storing the bottles in the dark minimized potential biases from varying light exposure across different experimental days. The entire workflow from migration experiment to hazard assessment is illustrated in Fig. S2.

### 2.4. Vacuum evaporation concentration (VEC) of samples

Of each bottle, 100 mL sample were evaporated at 55 °C, 20 mbar, using a VEC system (SyncorePlus Evaporator System, BUCHI Labor-technik AG, Switzerland). Up to 12 samples were evaporated in parallel for approximately 4 h until complete dryness, a process chosen to effectively reduce the high salt content in the extracts. Evaporating to dryness not only allows for a solvent change to 100 % MeOH, which aids in salt removal, but also provides more precise results compared to partial evaporation, which is challenging to control using a vacuum evaporator. The supernatants were recovered with glass pipettes and transferred to new 1.5 mL HPLC vials. Vials with salt residuals were weighed before and after evaporation to determine if MeOH losses were due to residual MeOH in the vial (no correction needed) or evaporation during the reconstitution process (requiring adjustment of the

enrichment factor). The final enrichment factor was 83 (100 mL enriched to 1.2 mL). After the last transfer, the samples were stored at  $-18^{\circ}\text{C}$  until analysis.

## 2.5. Quality assurance

For quality assurance, sample enrichment was performed on triplicate bottles. Each batch included at least two tap water blanks and one tap water sample was spiked with a mix of nine compounds at a final concentration of  $1\text{ }\mu\text{g/L}$  (Table S2). The recoveries of all spiked samples (nine samples distributed across eight batches) were used to evaluate the methods uncertainties. The relative standard deviation (RSD) ranged from 10 % to 23 % for most compounds, with the exception of octabenzene, which had a higher RSD of 34 %. Additionally, recovery experiments showed recoveries ranging from 42 % to 126 % for 13 compounds with analytical standard, with RSD between 9 % and 32 % ( $n = 9$  experimental replicates). The specified values are detailed in Table S3.

Additionally, one type of plastic bottle (Tritan clear bottles) was investigated in two different batches, with six replicates in total, to evaluate inter-batch variations for unknown features. The RSD was determined for 48 features detected above the peak intensity threshold of 1000 (Fig. S2). The intra-batch RSD for the triplicates in the first batch had a median of 12 %, and the triplicates in the second batch had a median of 13 %. The RSD for all samples between the batches was higher at 17 % but still within an acceptable range, allowing for comparison of bottle migration experiments conducted in different batches.

To minimize potential blank contamination, 16 enriched tap water blanks were included throughout the experiments and analytical sequence for blank correction. A feature was only retained if its peak intensity exceeded the highest blank peak intensity ( $n = 16$ ) by at least five times. Additionally, a triplicate filter was applied, requiring the feature to appear in all three experimental replicates with an RSD below 40 %. These combined filters reduced the number of detected features from 3300 to 690 in ESI+ and from 2500 to 315 in ESI-.

## 2.6. Chemical analysis

Analysis was carried out with LC coupled to electrospray ionization (ESI) quadrupole time-of-flight (QTOF) instrument. Detailed methods are available in [13]. Briefly, LC analysis was performed on an Acquity UPLC with a BEH C18 column ( $2.1 \times 100\text{ mm}$ ,  $1.7\text{ }\mu\text{m}$  pore size) from Waters at  $0.3\text{ mL/min}$  and injection volume of  $1\text{ }\mu\text{L}$ . The gradient program increased from 90 % eluent A (MilliQ  $\text{H}_2\text{O}$  + 0.1 % formic acid) to 99 % eluent B (acetonitrile + 0.1 % formic acid) over 16 min, held for 5 min. Samples were analysed on a G2-Si Synapt QTOF in data-independent MSe continuum mode (scan time 0.35 s; ramp trap collision energy 10–40 V) in both positive (ESI+) and negative (ESI-) modes, covering an  $m/z$  range of 50–1000.

## 2.7. Data processing

Data were processed and aligned using MS-DIAL (version 4.9), with parameters listed in Table S4. Each batch (ESI+ and ESI-) was processed individually. After feature detection and alignment, the feature list was exported to Excel for further processing. Features were filtered based on specific thresholds: the peak height needed to be higher than 1000 in at least triplicates of one sample, and the peak intensity in triplicate samples had to be at least five times the highest blank intensity for that feature. For blank filtration, all blanks from all batches were considered (16 blanks in total). Finally, the peak intensity among triplicates had to have a RSD of less than 40 % for at least one sample. Features not meeting these criteria were discarded to ensure confidence in removing potential blank compounds.

The filtered data were used for non-target analysis (NTA). A heatmap based on peak intensity was created in Excel without further scaling.

Additionally, the software MetaboAnalyst V 6.0 [14] was used to create a correlation heatmap. The data were auto-scaled (mean-centered and divided by the standard deviation of each variable) and a correlation heatmap was generated using hierarchical clustering and Pearson  $r$  distance measure. As the final NTA prioritization step, the homologous series detection tool was used with standard parameters [15] to find oligomers or homologous series with any length of repeating units in the samples.

For suspect screening, we used a compiled list of plastic monomers, additives and processing aids, which includes over 10,000 compounds [16]. The list was filtered to exclude inorganic substances and salts, which would provide incorrect CAS numbers for the salt free compound and sum formula. Correct CAS numbers were crucial for establishing a library with MS/MS data and ensuring unique identification. This resulted in a suspect library containing 6130 substances.

The confidence of the suspects was increased by comparing MS/MS spectra with the MassBank of North America (MoNA) or using in-silico spectra generated by the competitive fragmentation modeling (CFM) approach (Allen et al., 2015). Precursor and fragment matches had to be within 10 ppm. Compounds prioritized by NTA, without suspect library hits, were identified by accurate mass, with potential sum formulas assigned within 5 ppm. PubChem was used to identify plausible chemicals, and MS/MS library spectra were used for comparison, if available.

The confidence level scheme followed Schymanski et al. [17], requiring confidence level (CL) 1 or 2 for suspect screening identifications. CL 1 was achieved if it was confirmed with analytical standard. CL2 was achieved when the accurate mass matched ( $\pm 5\text{ ppm}$ ), fragments matched ( $\pm 20\text{ ppm}$ ) and the experimental retention time was within 2 min of the predicted RT. Retention time prediction was based on quantitative structure-property relationships (QSPR) [18]: A model was built using 140 compounds: 113 for training and 27 for testing. All test compounds were predicted correctly within a 2.8 min retention time window, with 94 % falling within 2.2 min

## 2.8. Quantitative non-target analysis (qNTA)

To quantify newly identified compounds without available analytical standards, concentrations were predicted using qNTA, employing QSPR as described previously [19]. This method predicts the response factor (peak intensity divided by concentration) for each compound using molecular descriptors. Concentration estimates were obtained by dividing the predicted response factor by the total peak intensity, accounting for isotopes, adducts, and known in-source fragments. The model was built for ESI+ and showed an average prediction error of 1.8 (fold change of predicted to observed response factor), with 27 out of 28 test compounds predicted within a factor 3. The initial model was trained on water-relevant compounds, expected to cover the chemical space of compounds in this study. The software Maestro 13.2 from Schrödinger, used for QSPR modelling, flagged compounds outside this chemical space, indicating higher prediction uncertainty. For compounds outside the chemical space, no predicted concentration was reported.

A drift correction was applied to ensure the models transferability from its initial development to the instruments performance at the time of analysis. The mean response difference of eight ions from five plastic-related standards was compared between the current study and the models development phase (Table S5). A response factor adjustment of 0.46 was applied to align the model with the current instrument conditions.

Analytical standards were available for six identified compounds, enabling validation of the prediction model tailored to plastic-relevant compounds. The standards were analyzed at  $100\text{ }\mu\text{g/L}$  and were predicted with the qNTA model, showing a median concentration error factor of 1.5 (Table 2). The largest deviation observed was for DEET, with an error factor of 1.9. Interestingly, for the two phthalates, the molecular ion  $[\text{M}+\text{H}]^+$  constituted less than 5 % of the total peak

**Table 2**

qNTA model performance - comparison of spiked concentration and predicted concentration based on sum peak intensity of molecular ion, adducts and in-source fragments.

	Actual concentration ( $\mu\text{g/L}$ )	Predicted concentration ( $\mu\text{g/L}$ )	Fold change error
Diethyltoluamide	100	190	1.9
Acetyl tributyl citrate	100	90	1.1
Tributyl citrate	100	170	1.7
Tris(2-butoxyethyl) phosphate	100	70	1.4
Diethyl phthalate	100	180	1.8
Dimethyl phthalate	100	110	1.1

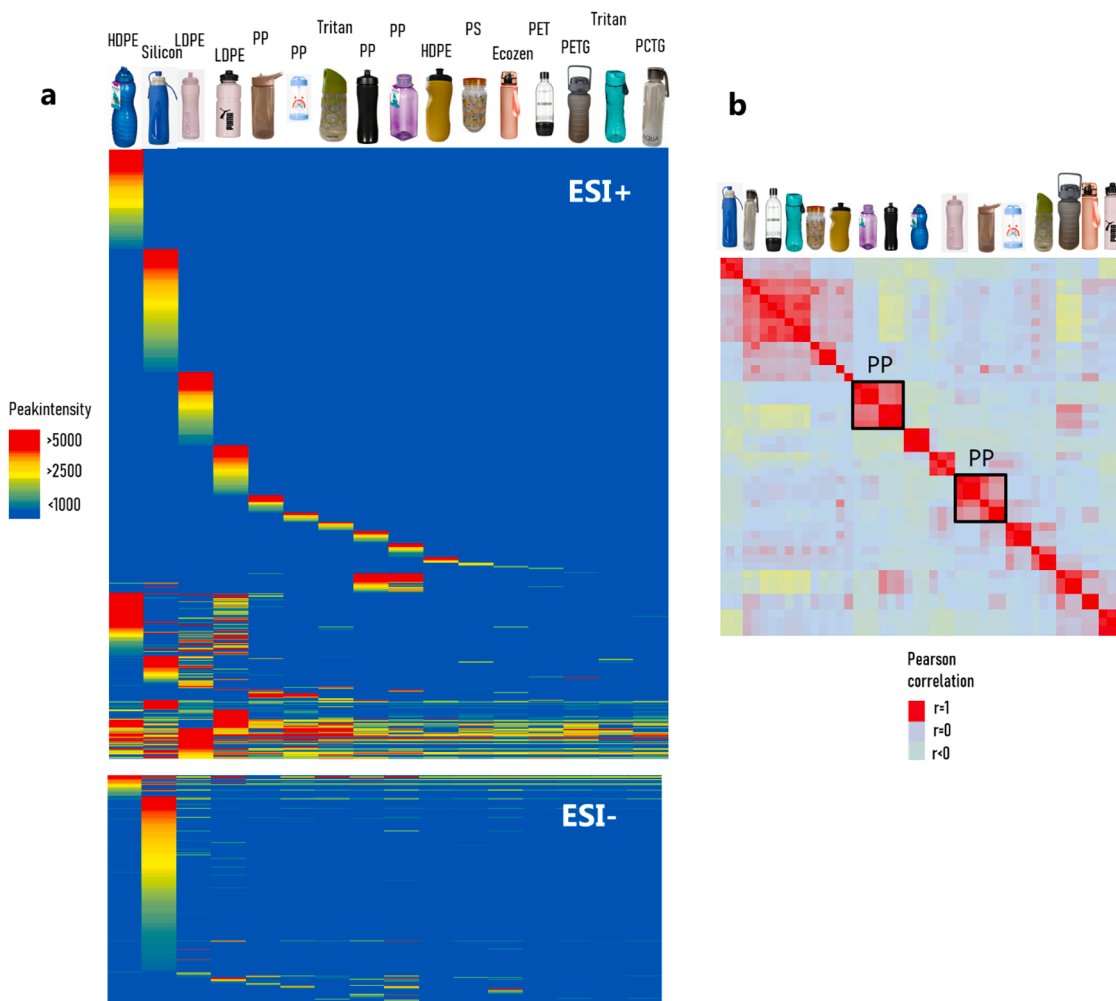
intensity. Without accounting for the in-source fragment and sodium ion, the predicted concentration error factor would have exceeded 20.

For compounds with available analytical standards, a two-point calibration was performed at 10 and 100  $\mu\text{g/L}$  (equivalent to 0.12 and 1.2  $\mu\text{g/L}$  for the 83 times enriched samples). Peaks were quantified if their intensity exceeded the threshold of 1000. All chemicals listed in Table 2 were detected in at least one sample, allowing for a detailed comparison between the qNTA approach and quantification based on analytical standards for real samples (Table S6). This comparison highlights the consistency of the predicted concentrations with those obtained from analytical standards, which was within a factor of two.

## 2.9. Toxicity assessment

To estimate the toxicity of the identified chemicals, a literature review was conducted. For most chemicals, the available toxicity data was either insufficient or ambiguous. The CompTox database provided toxicity test overviews for each compound, revealing significant discrepancies in threshold values. The lack of toxicity data for chemicals migrating from food contact materials (FCMs) is a widely recognized challenge. Due to this gap, toxicity in this study was estimated using predictive methods. These approaches, while helpful, are not a substitute for detailed risk assessments, as the available data remains limited and inconsistent. Consequently, assessing the actual human health impact of these migrating compounds -especially considering potential mixture effects- requires further research and more comprehensive data.

Cramer's rule was employed with Toxtree 3.1.0, which relates chemical structures to potential toxicity, dividing chemicals into three classes: Class I for low toxicity, Class II for intermediate toxicity and Class III for high toxicity [20]. The decision tree is organised by functional groups that suggest significant toxicity or reactivity. This approach is recommended for estimating the risk of FCM chemicals for human exposure and is commonly used for FCM toxicity evaluation [21, 22,10]. This method prioritizes compounds according to their hazard-ousness. Additionally, the toxicity estimation software tool (T.E.S.T) from the U.S. Environmental Protection Agency was used to estimate mutagenicity [23].



**Fig. 1.** a) Heatmap of the peak intensities for features detected in ESI+ (690 features) and ESI- (315 features); b) Correlation matrix for ESI+ and only features which were in more than one type of bottles. Correlation is shown for triplicate bottles.



### 3. Results and discussion

#### 3.1. Non-target analysis of drinking water stored in plastic bottles

Each type of bottle showed a unique chemical fingerprint, highlighting the complexity of assessing and managing chemical migration (Fig. 1). The chemical fingerprint was based on detected features, which are defined as distinct peaks detected by the chromatography system that corresponds to specific chemicals. In positive electrospray ionization (ESI+), 70 % (Fig. 1a), and in negative ESI (ESI-), 80 % of the detected features (Fig. 1b) were unique to individual bottles not appearing in any of the other 15 tested bottles. Minimal overlap was observed even among bottles made from same primary plastic materials. Only 16 out of 690 features detected in ESI+ mode were common across all 16 bottles (Table S7), highlighting the rarity of universally present chemical components. The high chemical diversity among reusable water bottles complicates prioritization, emphasizing the challenges in identifying leaching chemicals from plastic drinking bottles.

The blue silicone bottle was particularly remarkable with the highest number of unique features among the tested bottles. In ESI-, 70 % of all detected features were exclusive to this specific bottle. Data on migration of silicone materials under realistic usage conditions is limited [24–26]. Currently, there is no harmonized EU legislation for silicone materials used as FCMs [21]. Previous research has also indicated significant migration of unidentified compounds from silicone baby bottles [21]. Acrylates, used as cross-linkers in photo-curing processes, along with silicone oligomers, were previously identified by GC [27]. However, we did not confirm their presence in our study, indicating that the inclusion of volatile compounds could uncover an even broader spectrum of migration.

In our analysis, we did not find any features with more than three repeating units, excluding homologous series for the silicone bottles. No specific chemical group could explain the 450 unique features (ESI+ and ESI-) detected in these bottles. Interestingly, 143 of these features (ESI-) co-eluted at three distinct retention times, suggesting they likely correspond to only three compounds with substantial in-source fragmentation (Fig. S4). In-source fragmentation refers to the fragmentation of analytes during the initial ionization in the ESI source, before reaching the collision cell. This produces a molecular ion and multiple fragments from a single analyte, complicating the identification of the original compounds [28].

Bottles made of silicone, HDPE, LDPE, and PP showed the highest levels of chemicals. HDPE and LDPE bottles had heterogenic compound patterns with no correlation between bottles of the same material (e.g. HDPE blue and yellow, LDPE pink 1 and 2) (Fig. 1a,b). In contrast, the four PP bottles showed partial correlation. The black and purple PP samples, from New Zealand and Sweden respectively, shared 50 % of features, yielding a Pearson correlation coefficient of  $r > 0.5$  across all replicates (Fig. 1b). The clear and pink PP samples, both manufactured in Asia, shared 38 % of features, with a lower correlation ( $r > 0.25$ ). No significant correlation ( $0.1 < r < -0.2$ ) was observed between the two sets of PP samples.

Bottles made of PETG, PS, PET, and Tritan (blue) showed superior performance with less than 5 % of unknown features migrating into drinking water. Only seven features were unique to these materials. PETG and Ecozen had slightly higher migration, with 48 of 690 ESI+ features (6 %) migrating from each material and showing similar migration patterns ( $r = 0.5$ ). Both types were made in China and sold from the same shop in Denmark, indicating a manufacturer-specific chemical fingerprint.

These findings highlight the challenges regulatory agencies face in developing legislation to protect public health from chemical exposures via reusable water bottles. The significant variability in chemical compositions across different bottle types and materials complicates the establishment of effective and equitable regulations.

#### 3.2. Identification of chemicals migrating from plastic bottles

Table 3 provides an overview of all identified compounds, their concentrations, and hazard assessment.

##### 3.2.1. Phthalates

The blue silicone bottle, manufactured in China, showed migration of six phthalates: monomethyl phthalate (MMP), dimethyl phthalate (DMP), diethyl phthalate (DEP), diallyl phthalate (DAP), monohexyl phthalate (MHP), and mono(2-ethylhexyl) phthalate (MEHP). Di-n-propyl phthalate (DnPP) was identified, but inconclusive and with four times higher concentration migration in one bottle compared to the other two. Phthalates, used as plasticizers, can disrupt the endocrine system (Y. [30]). Low molecular weight phthalates like DEP can affect male and female reproductive health [31]. Popular high molecular weight phthalates, such as DEHP, have been more extensively studied for their toxicological effects (Y. [30]). However, this does not imply that lower molecular weight phthalates are less toxic. These smaller phthalates (<250 Da) may also be transformation products (TPs) of larger, more hydrophobic phthalates, which could go undetected by our method due to lower ionization sensitivity for hydrophobic compounds. Dibutyl phthalate (DBP) was excluded from the analysis due to blank contamination. In this study, MMP and MHP were reported for the first time as migrating from FCMs [32,33]. It is unknown if these compounds have been introduced as IAS or NIAS. These compounds may have been formed as transformation products of DMP and MEHP, respectively, through alkyl chain loss, a common biotic and abiotic reaction in phthalate degradation. Few compounds have been previously clarified in the text now that higher mass phthalates are more investigated, thus often con [34]. Phthalates were detected as sodium adducts or in-source fragments due to low molecular ion intensity. For compounds without available analytical standard (confidence level 5 in Table 1), the concentrations were predicted based on quantitative structure property relationships (QSPR) [29]. For the phthalates identified in ESI+, concentrations were 0.06 µg/L (DEP), 0.20 µg/L (DMP), and 0.35 µg/L (MMP). Concentrations for the remaining phthalates could not be estimated as they were detected only ESI- (the prediction model was only made for ESI+).

##### 3.2.2. Color agents

In the yellow HDPE bottle the compound 4-chloro-5-methyl-2-[[3-methyl-5-oxo-1-(3-sulphophenyl)-4H-pyrazol-4-yl]diazenyl]benzenesulfonic acid, also known as pigment yellow 191, was identified based on isotope pattern, plausible fragments and predicted retention time (eluted at 3.5 min and predicted at 3.9 min). Additionally, the brilliant toning red amine pigment 2-amino-4-chloro-5-methylbenzenesulfonic acid was identified in the same bottle. Interestingly, the brilliant toning red amine pigment was previously identified in groundwater in North Europe (Denmark) [19]. The yellow HDPE bottle was manufactured in North Europe as well (Sweden). Both, yellow and red pigments are concerning (Cramer Class III), but the concentration of the yellow pigment was 125 times higher (1.25 µg/L).

Anthraquinones are well-known for their use in blue-colored plastics, however, identifying the specific anthraquinone derivative used can be challenging [35]. In our study, the core structure, with all characteristic fragments of anthraquinone, was identified at three retention times (RT) in the blue HDPE bottle, suspected to be formed as in-source fragments from larger anthraquinones. The compound with the shortest RT (6.5 min) was also detected in the blue silica bottle.

##### 3.2.3. Sorbitol-based nuclear clarifying agents (NCAs)

NCAs were detected to migrate from all four investigated PP bottles. NCAs are increasingly used in polymer manufacturing to enhance optical clarity, physical attributes, and UV resistance, especially in polypropylene (PP) packaging, improving its visual appeal [36]. Dimethyldibenzylidene sorbitol (DMDBS) migrated from clear and pink

**Table 3**

Suspect compounds with concentration and predicted toxicity information. The confidence levels are according to [17]. Compounds with confidence level 1 were quantified based on analytical standard. For confidence level 2 the concentration was predicted according to [29]. A comparison between quantification of analytical standard and prediction model is shown in Table S6. TP=transformation product. Empty cells indicate that no information were available.

Compound name	CAS	Confidence level	Use	Concentration in drinking water from respective bottle	Hazard: Cramer Class III or mutagenicity**	Number in Regulation EC 10/2011 (with SML)
Brilliant toning red amine	88 –51 –7	1	Coloring	HDPE yellow (0.01 µg/L)	Class III	
Pigment yellow 191	129423 –54 –7	2	plastic	HDPE yellow (1.2 µg/L)*	Class III	
Anthraquinone derivatives	84 –65 –1	2		HDPE blue	Unknown	
	(anthraquinone)	(84 –65 –1)		Silicon blue		
Dimethyl phthalate (DMP)	131 –11 –3	1	Softening	Silicon blue (0.2 µg/L)		
Monomethyl phthalate (MMP)	4376 –18 –5	1	plasticizer	Silicon blue (0.35 µg/L)		
Diethyl phthalate DEP)	84 –66 –2	1		Silicon blue (0.06 µg/L)		
Monoethyl Phthalate (MHP)	24539 –57 –9	2		Silicon blue		
Diallyl phthalate (DAP)	131 –17 –9	2		Silicon blue		FCM 316 (ND***)
Mono(2-ethylhexyl) phthalate (MEHP)	4376 –20 –9	2		Silicon blue		
Dimethyldibenzylidene sorbitol (DMDBS)	135861 –56 –2	2	Clarifying agents	PP clear (9.9 µg/L)*	Class III	FCM 766 (-)
1,2,3-Trideoxy-4,6:5,7-bis-O-((4-propylphenyl)methylene)-nonitol (PBPS)	882073 –43 –0	2		PP pink (11.2 µg/L)* PP black (6.1 µg/L)* PP purple (4.1 µg/L)*	Class III, mutagenicity	FCM 808 (5 mg/kg)
Di-p-methylbenzylidenesorbitol (MDBS)	87826 –41 –3	2		PP purple (3.7 µg/L)*	Class III	FCM 752 (-)
1-(2-Hydroxyethyl)-2,2,6,6-tetramethylpiperidin-4-ol	52722 –86 –8	2	light aging inhibitor	PP black (3.5 µg/L)*	Class III	
Bisphenol A bis(2,3-dihydroxypropyl) ether (BADGE.2H2O)	5581 –32 –8	2	Epoxy coating derivative	PP black (0.2 µg/L)*	Class III	
Bisphenol A (2,3-dihydroxypropyl) glycidyl ether (BADGE.H2O)	76002 –91 –0	2		PP purple (0.33 µg/L)* PP black (0.24 µg/L)*	Class III	
Diphenyl sulphone	127 –63 –9	2	Potential TP coating	Silicon blue (0.05 µg/L)* HDPE blue (0.01 µg/L)* LDPE pink1 (0.01 µg/L)*	Class III	FCM 313 (3 mg/kg)
2-allylphenol	1745 –81 –9	2	Intermediate	Silicon blue (0.02 µg/L)*		
Vanillin	121 –33 –5	2		Silicon blue (0.33 µg/L)*		
4-Acetoxystyrene	2628 –16 –2	2		Silicon blue (0.11 µg/L)*		
Methyl 2-hydroxy-3-methylbenzoate	23287 –26 –5	2		Silicon blue (0.05 µg/L)*		
Ethyl 2,4,6-trimethylbenzoate	1754 –55 –8	2		Silicon blue (0.01 µg/L)*		
M-Toluylic acid	99 –04 –7	2		Silicon blue (0.14 µg/L)*		
3,3,5-Trimethylcyclohexanone	873 –94 –9	2		Silicon blue (0.08 µg/L)*		
4-Tert-butylbenzoic acid	98 –73 –7	2		Silicon blue (1.51 µg/L)*		
Lauro lactam	947 –04 –6	1		Silicon blue (0.02 µg/L)	Class III	FCM 382 (5 mg/kg)
Diethyltoluamide	134 –62 –3	1	Plasticizer related	Silicon blue (0.05 µg/L) LDPE pink1 (0.02 µg/L) HDPE blue (0.01 µg/L)		
1-Naphthol	90 –15 –3	2	Processing aid	Silicon blue (0.05 µg/L)*	mutagenicity	
Acetyl tributyl citrate	77 –90 –7	1	Plasticizer	Ecozen salmon (0.19 µg/L) LDPE pink1 (0.15 µg/L) Silicon blue (0.13 µg/L)		FCM 138 (-)
Tributyl citrate	77 –94 –1	1		LDPE pink1 (2.92 µg/L)	Class III	
Tris(2-butoxyethyl) phosphate	78 –51 –3	1		HDPE blue (0.02 µg/L) LDPE pink1 (0.01 µg/L)	Class III	
Proline	147 –85 –3	2	Dispersion agent	Tritan clear		
Triphenylphosphine oxide	791 –28 –6	1	TP plasticizer	Ecozen salmon (0.2 µg/L)	Class III	
Lauramine oxide O2		4		Tritan clear		
Myristamine oxide O2		4		Tritan clear		
Lauramine oxide	1643 –20 –5	2	Plasticizer	Tritan clear	Class III	
Myristamine oxide	3332 –27 –2	2		Tritan clear	Class III	
Polyethylene Glycols (PEGs)		2	Chain extender	LDPE pink 2 (Σ 48 µg/L)*		
Methoxypolyethylene Glycols (mPEGs)		2		HDPE blue (Σ 6 µg/L)*		
Polypropylene Glycols (PPGs)		2	Modifier	HDPE blue LDPE pink 2		
EO/PO copolymers		2		HDPE blue LDPE pink 2		
PEG+PPG+alkyl group		2		LDPE pink 1 HDPE blue		
Neopentyl glycols		2	Stabilizer	HDPE blue		

\* concentration was predicted via QSPR model

\*\* mutagenicity was predicted by T.E.S.T from the U.S. Environmental Protection Agency. If the cell is empty, no hazard was predicted by T.E.S.T and/or Cramer rules

\*\*\* the substance shall not migrate in detectable quantities (Commission Regulation (EU) No 10/2011)

PP bottles at concentrations between 8 and 9  $\mu\text{g/L}$ . 1,2,3-Trideoxy-4,6:5,7-bis-O-((4-propylphenyl)methylene)-nonitol (PBPS) migrated from black and purple PP bottles at concentrations between 3 and 5  $\mu\text{g/L}$ . Di-p-methylbenzylidenesorbitol (MDBS) was detected migrating only from purple PP bottles at 3  $\mu\text{g/L}$ . Due to lack of analytical standards, research on these compounds is limited [36]. The NCAs are concerning due to their high predicted toxicity (Cramer Class III) and potential mutagenicity, coupled with the high concentrations detected in the stored drinking water of PP bottles. All detected NCAs are listed in the positive additives list of EU Regulation No. 10/2011 (MDBS as FCM No. 752, DMDBS as FCM No. 766, PBPS as FCM No. 808)(EU, 2011). While no specific migration limits (SMLs) are defined for FCM Nos. 752 and 766, FCM No. 808 has an SML of 5  $\text{mg/kg}$  in food.

### 3.2.4. Bisphenol A-diglycidyl ether (BADGE) derivatives

BADGE, derived from bisphenol A (BPA), is widely utilized as a coating material. Although BADGE itself was not found in the samples, its derivatives, Bisphenol A (2,3-dihydroxypropyl) ether (BADGE-2H<sub>2</sub>O) and glycidyl ether (BADGE-H<sub>2</sub>O) were detected in the black and purple PP bottles. It is unknown whether the bottles have been treated with specific coatings or adhesives, or if the compounds were introduced as NIAS. While BPA is known for its endocrine-disrupting effects, studies on BADGE derivatives remain inconclusive, suggesting varying levels of toxicity (D. [37]). There is evidence that BADGE-2H<sub>2</sub>O exhibits estrogenic activity, disrupting testicular steroidogenesis similar to BPA (D. [37]). Although BADGE and its derivatives were initially banned under Directive 2002/16/EC, EFSA later reviewed toxicity data and, since Regulation 1895/2005, allowed its use with a specific migration limit (SML) of 9  $\text{mg/kg}$  in food [38]. From the black PP bottle, a total of 0.4  $\mu\text{g/L}$  of BADGE derivatives was migrating, and from the purple PP bottle 0.33  $\mu\text{g/L}$  of BADGE-H<sub>2</sub>O was detected. Even higher migration is expected for more lipophilic liquids than water. Wiesinger et al. [16]

included BADGE among the plastic additives used in PP bottles, which was also confirmed in this study.

### 3.2.5. Intermediates and plasticizer

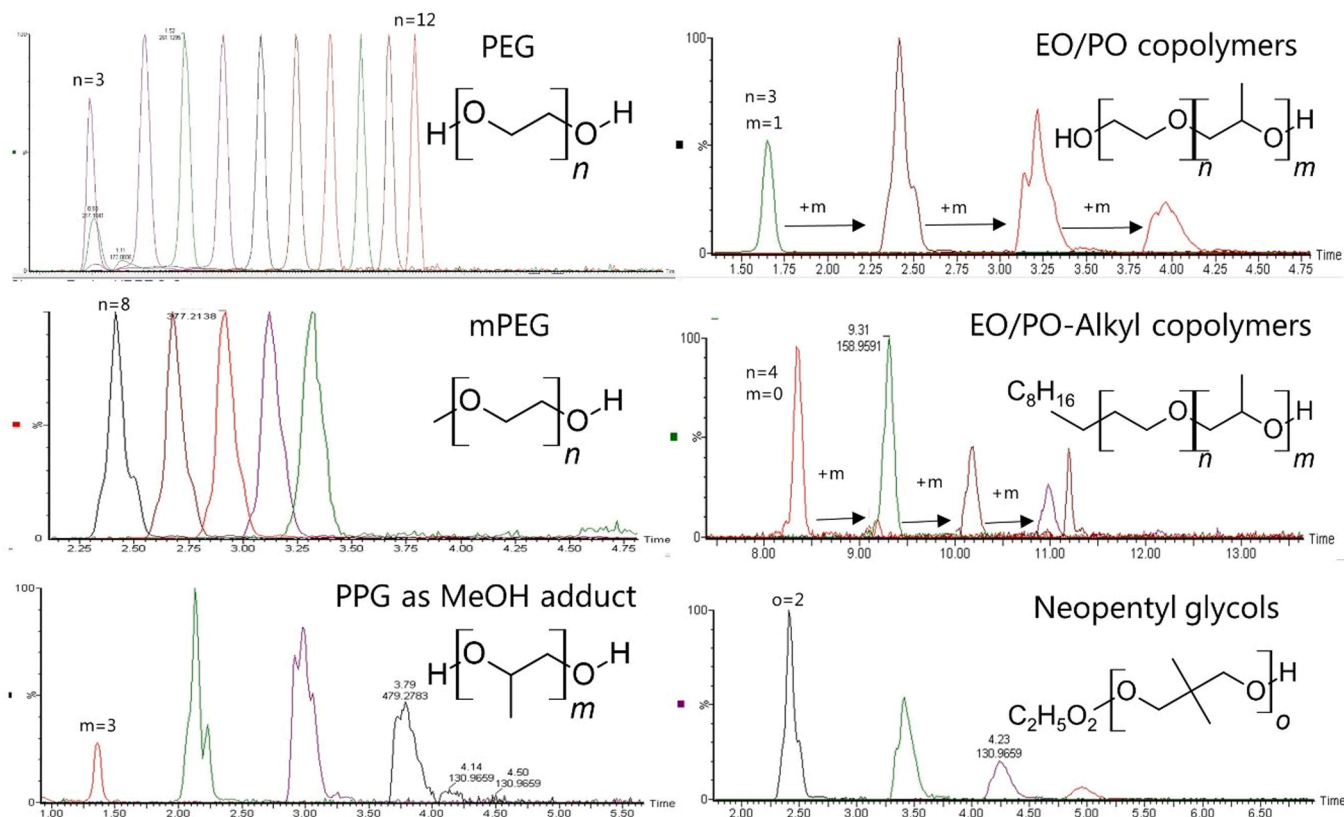
In the blue silicone bottle, various intermediates used in plastic production were detected [16], including 1-allylphenol, vanillin, 4-acetoxystyrene, methyl 2-hydroxy-3-methylbenzoate, ethyl 2,4,6-trimethylbenzoate, and m-Toluic acid. Notably, m-Toluic acid, primarily a precursor for DEET [39] was found alongside DEET itself. This is not the first time that DEET was proven to migrate from reusable plastic bottles [10], suggestion its dual role as an insect repellent and plasticizer. Literature shows that DEET can be used as a plasticizer [40] but the applications remain unknown.

In HDPE pink 1, plasticizers acetyl tributyl citrate, tributyl citrate and tris(2-butoxyethyl) phosphate (TBEP) were detected. TBEP was detected with higher peak intensity in the blue HDPE bottle (0.02  $\mu\text{g/L}$ ). TBEP inhibits cell profiling [41]. The Ecozen bottle contained tributyl citrate and the plasticizer TP triphenylphosphine oxide. In the blue silicone bottle, the plasticizer lauro lactam and intermediates 1-naphtol, 3,3,5-Trimethylcyclohexanone, and 4-tert-butylbenzoic acid were detected, up to 1.5  $\mu\text{g/L}$ .

### 3.2.6. Oligomers

From the 690 ESI+ and 315 ESI- features, repeating units were assigned to 72 and 10 features, respectively, indicating oligomers play a minor role in the migration number of unknowns from the bottles. Six homologous series were identified (Fig. 2 and Table S8) migrating from three bottles: HDPE blue, LDPE pink 1, and LDPE pink 2.

Polyethylene glycols (PEGs) with sum formula  $\text{C}_{2n}\text{H}_{4n+2}\text{O}_{n+1}$  were detected from  $n = 3$  to  $n = 12$  in the Pink LDPE 2 bottles, and methoxy-PEGs (mPEGs) from  $n = 8$  to  $n = 12$  in the blue HDPE bottle, all ionizing as sodium adducts. Their structures were confirmed by detecting



**Fig. 2.** Extracted ion chromatograms of the detected oligomers. All identified oligomers were detected as sodium adduct and contained repeating units of polyethylene glycols (PEGs), polypropylene glycols (PPGs) or neopentyl glycols.

repeating units as fragments (e.g.  $m/z$  89.0579, 133.0869). PEGs are used as chain extenders to enhance polymer properties such as stability, degradability, and permeability [42]. Vallejos et al., [43] reported the use of PEGs and derivatives, such as mPEG, in PE formulations as antistatic agents. PEGs are approved by the US Food and Drug Administration (FDA) for human use as non-toxic polyethers [44] and have been detected in several food migration studies involving plastic FCMs [32, 33]. However, the high concentrations of PEGs migrating into water in this study are concerning, totalling in 48  $\mu\text{g/L}$  PEG and 6  $\mu\text{g/L}$  mPEG for the pink LDPE 2 and blue HDPE bottle, respectively. The total concentration was calculated by predicting the concentration of each compound individually and then summing the results.

In both bottles (LDPE pink 2 and HDPE blue), polypropylene glycols (PPGs) were identified as MeOH-sodium adducts. PPGs without MeOH adducts correlated in relative peak intensity with the higher signals of MeOH adducts, suggesting that MeOH attachment occurred during analysis and was not part of the bottle migration itself. This observation is consistent with previous findings that oligomers frequently form adducts with methanol (MeOH) [10]. Recently, PPGs were also detected in food cooked in microwavable plastic containers [45]. PPGs are used to improve plastic properties and are considered safe additives [45]. Concentrations could not be estimated in this study, as the prediction model was not trained for compounds forming MeOH adducts.

In both, pink LDPE 2 and HDPE blue bottles, ethylene oxide/propylene oxide (EO/PO) copolymers were detected, with PEG  $n = 3$  and different amounts of PPG (from  $n = 1$  to  $n = 4$ ). EO/PO copolymers modify material composition, such as promoting the migration of natural antioxidant like tocopherol [42]. Tocopherol was not detected in this study, so the purpose of EO/PO copolymers in the bottles remains unknown. Additionally, EO/PO copolymers linked to an alkyl chain ( $\text{C}_8\text{H}_{16}$ ) were detected, with retention times of 8–11 min compared to 1.5–4 min for pure EO/PO copolymers. Fragments of both PPG and PEG repeating units were observed. These compounds are typically reported in cosmetics, not FCMs [46]. However, cosmetics and FCMs often share compounds to enhance safety, barrier properties, and control hydrophobicity (non-ionic surfactants) [36].

Neopentyl glycol oligomers (NPGs) with ethylene glycol as an end group were detected only in the blue HDPE bottle. Identified by their repeating unit ( $\text{C}_5\text{H}_{10}\text{O}_2$ ), NPGs are known to be used in PET as main and co-monomers [47]. Recently, NPGs were also found as oligomers in other plastics including PET, PETG and Tritan™ [48]. Our study indicates their presence in HDPE material.

### 3.2.7. Further compounds and limitations of compound detection

1-(2-Hydroxyethyl)-2,2,6,6-tetramethylpiperidin-4-ol (HE-TMP), a light aging inhibitor, was found in the black PP bottle at 3.5  $\mu\text{g/L}$ . Although, no literature is available for this compound, toxicity predictions flagged it as a potential mutagen, and it was also in Cramer class III. In the clear Tritan bottle, the surfactants lauramine oxide and myristamine oxide were detected. Two additional molecules with similar fragment patterns, but with two more oxygen atoms, likely transformation products (TPs) of the amine oxides, were also identified. Their concentrations could not be predicted due to their structures falling outside the models chemical space. Despite being classified as Cramer Class III, these compounds are used in cosmetic and household products [49]. Additionally, the dispersing agent proline, classified as Cramer Class I, was detected in the same bottle. Diphenyl sulfone, detected in blue HDPE and pink LDPE 1, could serve various purposes (e.g., thermal or light stabilizer, flame retardant, plasticizer) or be a byproduct of bisphenol S [50].

This study focused on non-volatile and semi-volatile compounds, as defined by the workflow (VEC for sample enrichment and LC-ESI-HRMS for analysis). Volatile organic compounds (VOCs) were not included in this workflow, though their inclusion could provide further insights into migration patterns, particularly related to polymer oligomers, such as those found in silicone materials [24]. Additionally, using acidic food

simulants (e.g., to mimic juice or soft drinks) instead of drinking water could have led to different migration behaviors. During data processing, the strict blank filtering applied ensured the exclusion of false-positive chemical identifications; however, this may have resulted in the omission of some expected migrating compounds from food contact materials (FCMs), such as antioxidants, which previous studies have shown can be masked by blank contaminants [51]. Fig. 3.

### 3.3. Hazard evaluation of the plastic bottles

Based on suspect and non-target analysis, hazard estimates were made for identified and quantified chemicals. Bottles made of PP, PE, and silicone posed the highest risk. PP bottles leached 65–85 chemicals, including clarifying agents (up to 10  $\mu\text{g/L}$ ), BADGE derivatives, and the light inhibitor HE-TMP (3.5  $\mu\text{g/L}$ ). The silicone bottle accounted for 60 % of detected features, including phthalates and plasticizers, though over 97 % of the features remain unidentified. The blue HDPE bottle contained anthraquinone derivatives and plasticizers, while the yellow HDPE bottle had fewer migrations but high levels of pigment yellow. Two pink LDPE bottles revealed over 200 unknowns and in addition tributyl citrate and PEGs (>40  $\mu\text{g/L}$ ).

In contrast, plastic bottles made of PCTG, PS, Tritan, PETG, and PET performed better, with LC-ESI-HRMS detecting only 6 % of all features. The clear Tritan bottle leached 70 features (10 %) in ESI+, compared to 35 from the blue Tritan, with low-risk compounds like proline and surfactants detected. Ecozen bottles had lower migration rates (5 %) but released concerning chemicals, including acetyl tributyl citrate and triphenylphosphate oxide (Cramer Class III).

While Kim et al. [52] identified PE as the most concerning material through targeted analysis, our findings suggest that PP and silicone materials also pose significant risks when broader screening is conducted.

## 4. Conclusion

This study reveals significant variability in the chemical profiles of water stored in plastic bottles under common user scenarios. Of nearly 1000 unknown compounds, more than 70 % were unique to specific bottle types. Silicone, HDPE, LDPE, and PP bottles exhibited the highest rates of chemical migration into tap water stored in the bottles for 24 h, while PS, PET, PETG, and PCTG bottles showed minimal migration, indicating lower health hazard. These findings emphasize that current compound classes used for evaluating especially PP and silicone bottles are insufficient, highlighting underestimated risks. There was low correlation between country of origin and chemical diversity, with high variability across bottles. Clear bottles were preferred due to reduced colorant leaching. This study demonstrated the advantages of broad screening approaches to pinpoint materials with high chemical migration. However, for a comprehensive risk assessment, established limit values are necessary. These values are still lacking due to the absence of detailed toxicity information, leaving toxicity assessments largely reliant on predictions.

### CRedit authorship contribution statement

**Selina Tisler:** Writing – original draft, Visualization, Validation, Supervision, Data curation, Conceptualization. **Nastacha Kristiansen:** Writing – review & editing, Methodology, Conceptualization. **Jan H. Christensen:** Writing – review & editing, Supervision, Resources, Conceptualization.

### 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.



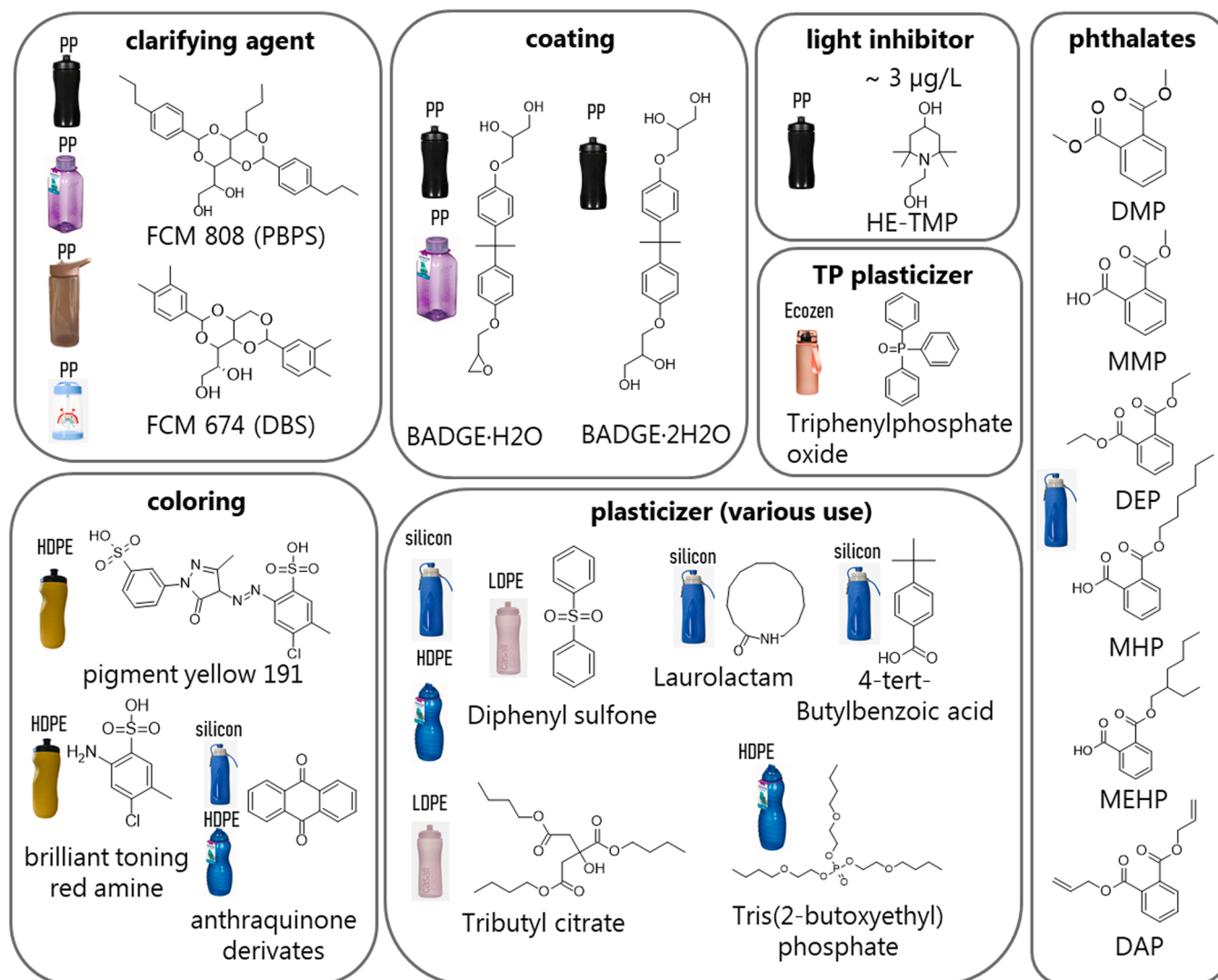


Fig. 3. Overview about the most concerning chemicals detected in drinking water (either toxicity information from literature or predicted in Cramer Class III), migrated from the respective plastic bottle.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at [doi:10.1016/j.jhazmat.2024.136391](https://doi.org/10.1016/j.jhazmat.2024.136391).

## Data availability

Data will be made available on request.

## References

- [1] Coelho, P.M., Corona, B., ten Klooster, R., Worrell, E., 2020. Sustainability of reusable packaging—Current situation and trends. *Resour. Conserv. Recycl.* X 6, 100037. <https://doi.org/10.1016/j.rcrx.2020.100037>.
- [2] Greenwood, S.C., Walker, S., Baird, H.M., Parsons, R., Mehl, S., Webb, T.L., Slark, A.T., Ryan, A.J., Rothman, R.H., 2021. Many Happy Returns: Combining insights from the environmental and behavioural sciences to understand what is required to make reusable packaging mainstream. *Sustain. Prod. Consum.* 27, 1688–1702. <https://doi.org/10.1016/j.spc.2021.03.022>.
- [3] Kato, L.S., Conte-Junior, C.A., 2021. Safety of Plastic Food Packaging: The Challenges about Non-Intentionally Added Substances (NIAS) Discovery, Identification and Risk Assessment. *Polymers* 13 (13), 2077. <https://doi.org/10.3390/polym13132077>.
- [4] Groh, K.J., Geueke, B., Martin, O., Maffini, M., Muncke, J., 2021. Overview of intentionally used food contact chemicals and their hazards. In: *Environment International*, 150. Elsevier Ltd., <https://doi.org/10.1016/j.envint.2020.106225>.
- [5] Bhunia, K., Sablani, S.S., Tang, J., Rasco, B., 2013. Migration of chemical compounds from packaging polymers during microwave, conventional heat treatment, and storage. *Compr. Rev. Food Sci. Food Saf.* 12 (5), 523–545. <https://doi.org/10.1111/1541-4337.12028>.
- [6] Daniel, J., Hoetzer, K., McCombie, G., Grob, K., 2019. Conclusions from a Swiss official control of the safety assessment for food contact polyolefins through the compliance documentation of the producers. *Food Addit. Contam. - Part A Chem., Anal. Control, Expo. Risk Assess.* 36 (1), 186–193. <https://doi.org/10.1080/19440049.2018.1556405>.
- [7] Muncke, J., 2011. Endocrine disrupting chemicals and other substances of concern in food contact materials: An updated review of exposure, effect and risk assessment. *J. Steroid Biochem. Mol. Biol.* 127 (s 1–2), 118–127. <https://doi.org/10.1016/j.jsbmb.2010.10.004>.
- [8] Muncke, J., Backhaus, T., Geueke, B., Maffini, M.V., Martin, O.V., Myers, J.P., Soto, A.M., Trasande, L., Trier, X., Scheringer, M., 2017. Scientific challenges in the risk assessment of food contact materials. In: *Environmental Health Perspectives*, 125. Public Health Services, US Dept of Health and Human Services, <https://doi.org/10.1289/EHP644>.
- [9] Zimmermann, L., Scheringer, M., Geueke, B., Boucher, J.M., Parkinson, L.V., Groh, K.J., Muncke, J., 2022. Implementing the EU Chemicals Strategy for Sustainability: The case of Food Contact Chemicals of Concern. *J. Hazard. Mater.* 129167. <https://doi.org/10.1016/j.jhazmat.2022.129167>.
- [10] Tisler, S., Christensen, J.H., 2022. Non-target screening for the identification of migrating compounds from reusable plastic bottles into drinking water. *J. Hazard. Mater.* 429. <https://doi.org/10.1016/j.jhazmat.2022.128331>.
- [11] Stiles, R., Yang, I., Lippincott, R.L., Murphy, E., Buckley, B., 2007. Potential sources of background contaminants in solid phase extraction and microextraction. *J. Sep. Sci.* 30 (7), 1029–1036. <https://doi.org/10.1002/jssc.200600358>.
- [12] Mechelke, J., Longrée, P., Singer, H., Hollender, J., 2019. Vacuum-assisted evaporative concentration combined with LC-HRMS/MS for ultra-trace-level

- screening of organic micropollutants in environmental water samples. *Anal Bioanal Chem.* <https://doi.org/10.1007/s00216-019-01696-3>.
- [13] Tisler, S., Tüchsen, P.L., Christensen, J.H., 2022. Non-target screening of micropollutants and transformation products for assessing AOP-BAC treatment in groundwater. *Environ Pollut* 309. <https://doi.org/10.1016/j.envpol.2022.119758>.
- [14] Xia, J., Psychogios, N., Young, N., Wishart, D.S., 2009. MetaboAnalyst: a web server for metabolomic data analysis and interpretation. *Nucleic Acids Res* 37 (Web Server), W652–W660. <https://doi.org/10.1093/nar/gkp356>.
- [15] Loos, M., Singer, H., 2017. Nontargeted homologue series extraction from hyphenated high resolution mass spectrometry data. *J Chemin-* 9 (1), 12. <https://doi.org/10.1186/s13321-017-0197-z>.
- [16] Wiesinger, H., Wang, Z., Hellweg, S., 2021. Deep Dive into Plastic Monomers, Additives, and Processing Aids. *Environ Sci Technol* 55 (13), 9339–9351. <https://doi.org/10.1021/acs.est.1c00976>.
- [17] Schymanski, E.L., Jeon, J., Gulde, R., Fenner, K., Ruff, M., Singer, H.P., Hollender, J., 2014. Identifying small molecules via high resolution mass spectrometry: Communicating confidence. *Environ Sci Technol* 48 (4), 2097–2098. <https://doi.org/10.1021/es5002105>.
- [18] Tisler, S., Engler, N., Jørgensen, M.B., Kilpinen, K., Tomasi, G., Christensen, J.H., 2022. From data to reliable conclusions: Identification and comparison of persistent micropollutants and transformation products in 37 wastewater samples by non-target screening prioritization. *Water Res* 219. <https://doi.org/10.1016/j.watres.2022.118599>.
- [19] Tisler, S., Skribic, N., Reinhardt, L.M., Albrechtsen, H.-J., & Christensen, J.H. (2024). A non-target evaluation of drinking water contaminants in pilot scale activated carbon and anion exchange resin treatments. *Manuscript Under Review (Water Research)*.
- [20] Kroes, R., Renwick, A.G., Cheeseman, M., Kleiner, J., Mangelsdorf, I., Piersma, A., Schilter, B., Schlatter, J., van Schothorst, F., Vos, J.G., Würtzen, G., 2004. Structure-based thresholds of toxicological concern (TTC): guidance for application to substances present at low levels in the diet. *Food Chem Toxicol* 42 (1), 65–83. <https://doi.org/10.1016/j.fct.2003.08.006>.
- [21] da Silva Oliveira, W., Ubada, S., Nerín, C., Padula, M., Teixeira Godoy, H., 2019. Identification of non-volatile migrants from baby bottles by UPLC-Q-TOF-MS. *Food Res Int* 123, 529–537. <https://doi.org/10.1016/j.foodres.2019.05.012>.
- [22] García Ibarra, V., Rodríguez Bernaldo de Quirós, A., Paseiro Losada, P., Sendón, R., 2018. Identification of intentionally and non-intentionally added substances in plastic packaging materials and their migration into food products. *Anal Bioanal Chem* 410 (16), 3789–3803. <https://doi.org/10.1007/s00216-018-1058-y>.
- [23] U.S. Environmental Protection Agency. (2022). *Toxicity Estimation Software Tool (TEST) Version 5.1.2*. <https://www.epa.gov/comptox-tools/toxicity-estimation-software-tool-test>.
- [24] Asensio, E., Uranga, J., Nerín, C., 2022. Analysis of potential migration compounds from silicone molds for food contact by SPME-GC-MS. *Food Chem Toxicol* 165, 113130. <https://doi.org/10.1016/j.fct.2022.113130>.
- [25] Feng, D., Li, X., Fan, X., Guo, Y., Zhang, J., Yuan, H., Wang, W., Zhao, T., Han, T., 2023. Cytotoxicity, endocrine disrupting activity, and chemical analysis of 42 food contact silicone rubber products. *Sci Total Environ* 872, 162298. <https://doi.org/10.1016/j.scitotenv.2023.162298>.
- [26] SZABÓ, B.S., JAKAB, P.P., HEGEDŰS, J., KIRCHKESZNER, C., PETROVICS, N., NYIRI, Z., BODAI, Z., RIKKER, T., EKE, Z., 2021. Determination of 24 primary aromatic amines in aqueous food simulants by combining solid phase extraction and salting-out assisted liquid–liquid extraction with liquid chromatography tandem mass spectrometry. *Microchem J* 164, 105927. <https://doi.org/10.1016/j.microc.2021.105927>.
- [27] Liu, Y.-Q., Wrona, M., Su, Q.-Z., Vera, P., Nerín, C., Hu, C.-Y., 2021. Influence of cooking conditions on the migration of silicone oligomers from silicone rubber baking molds to food simulants. *Food Chem* 347, 128964. <https://doi.org/10.1016/j.foodchem.2020.128964>.
- [28] Giera, M., Aisporna, A., Uritboonthai, W., Siuzdak, G., 2024. The hidden impact of in-source fragmentation in metabolic and chemical mass spectrometry data interpretation. *Nat Metab.* <https://doi.org/10.1038/s42255-024-01076-x>.
- [29] Tisler, S., Kilpinen, K., Pattison, D.I., Tomasi, G., Christensen, J.H., 2024. Quantitative Nontarget Analysis of CECs in Environmental Samples Can Be Improved by Considering All Mass Adducts. *Anal Chem* 96 (1), 229–237. <https://doi.org/10.1021/acs.analchem.3c03791>.
- [30] Wang, Y., Qian, H., 2021. Phthalates and Their Impacts on Human Health. *Healthcare* 9 (5), 603. <https://doi.org/10.3390/healthcare9050603>.
- [31] Weaver, J.A., Beverly, B.E.J., Keshava, N., Mudipalli, A., Arzuaga, X., Cai, C., Hotchkiss, A.K., Makris, S.L., Yost, E.E., 2020. Hazards of diethyl phthalate (DEP) exposure: A systematic review of animal toxicology studies. *Environ Int* 145, 105848. <https://doi.org/10.1016/j.envint.2020.105848>.
- [32] FPF. (2022). *FCCmigex Database*. <https://www.foodpackagingforum.org/resources/fccmigex>.
- [33] Geueke, B., Groh, K.J., Maffini, M.V., Martin, O.V., Boucher, J.M., Chiang, Y.-T., Gwosdz, F., Jieh, P., Kassotis, C.D., Łańska, P., Myers, J.P., Odermatt, A., Parkinson, L.V., Schreier, V.N., Srebny, V., Zimmermann, L., Scheringer, M., Muncke, J., 2023. Systematic evidence on migrating and extractable food contact chemicals: Most chemicals detected in food contact materials are not listed for use. *Crit Rev Food Sci Nutr* 63 (28), 9425–9435. <https://doi.org/10.1080/10408398.2022.2067828>.
- [34] Kaur, R., Kumari, A., Rajput, V.D., Minkina, T., Kaur, R., 2023. Biodegradation of phthalates and metabolic pathways: an overview. *Environ Sustain* 6 (3), 303–318. <https://doi.org/10.1007/s42398-023-00268-7>.
- [35] Key, S., Ryan, P.G., Gabbott, S.E., Allen, J., Abbott, A.P., 2024. Influence of colourants on environmental degradation of plastic litter. *Environ Pollut* 347, 123701. <https://doi.org/10.1016/j.envpol.2024.123701>.
- [36] Tsochatzis, E.D., Theodoridis, G., Gika, H.G., 2021. Development and Validation of a UHPLC-qTOF MS Method for the Determination of Sorbitol-Based Nuclear Clarifying Agents in Food Simulants after Migration from Food Contact Materials. *Appl Sci* 11 (9), 3789. <https://doi.org/10.3390/app11093789>.
- [37] Wang, D., Zhao, H., Fei, X., Synder, S.A., Fang, M., Liu, M., 2021. A comprehensive review on the analytical method, occurrence, transformation and toxicity of a reactive pollutant: BADGE. *Environ Int* 155, 106701. <https://doi.org/10.1016/j.envint.2021.106701>.
- [38] EU. (2020). *Restriction of epoxy derivatives in food contact materials*. Regulation (EC) No 1895/2005. <https://eur-lex.europa.eu/EN/legal-content/summary/restriction-of-epoxy-derivatives-in-food-contact-materials.html>.
- [39] Pham, D.T., Nguyen, V.T., Vu, B.D., Phan, D.C., 2022. A New Method for the Synthesis of N,N-Diethyl-m-Methylbenzamide from m-Toluic Acid and Diethylamine Using 1,1'-Carbonyl-di-(1,2,4-triazole) (CDT) as Coupling Agent. *Lett Org Chem* 19 (9), 766–769. <https://doi.org/10.2174/157017861866621119121227>.
- [40] Di Lorenzo, M.L., Longo, A., 2019. N,N-Diethyl-3-methylbenzamide (DEET): A mosquito repellent as functional plasticizer for poly(L-lactic acid). *Thermochim Acta* 677, 180–185. <https://doi.org/10.1016/j.tca.2019.02.004>.
- [41] Simonetti, G., Riccardi, C., Pomata, D., Acquaviva, L., Fricano, A., Buirelli, F., Senofonte, M., Di Filippo, P., 2024. Studies of Potential Migration of Hazardous Chemicals from Sustainable Food Contact Materials. *Foods* 13 (5), 645. <https://doi.org/10.3390/foods13050645>.
- [42] Castro López, M. del M., Dopico García, S., Ares Pernas, A., López Vilarino, J.M., González Rodríguez, M.V., 2012. Effect of PPG-PEG-PPG on the Tocopherol-Controlled Release from Films Intended for Food-Packaging Applications. *J Agric Food Chem* 60 (33), 8163–8170. <https://doi.org/10.1021/jf301442p>.
- [43] Vallejos, S., Trigo-López, M., Arnaiz, A., Miguel, A., Muñoz, A., Mendía, A., García, J.M., 2022. From Classical to Advanced Use of Polymers in Food and Beverage Applications. *Polymers* 14 (22), 4954. <https://doi.org/10.3390/polym14224954>.
- [44] Li, X., Loh, X.J., Wang, K., He, C., Li, J., 2005. Poly(ester urethane)s Consisting of Poly[(R)-3-hydroxybutyrate] and Poly(ethylene glycol) as Candidate Biomaterials: Characterization and Mechanical Property Study. *Biomacromolecules* 6 (5), 2740–2747. <https://doi.org/10.1021/bm050234g>.
- [45] Díaz-Galiano, F.J., Gómez-Ramos, M.J., Beraza, I., Murcia-Morales, M., Fernández-Alba, A.R., 2023. Cooking food in microwavable plastic containers: in situ formation of a new chemical substance and increased migration of polypropylene polymers. *Food Chem* 417, 135852. <https://doi.org/10.1016/j.foodchem.2023.135852>.
- [46] Fiume, M.M., Heldreth, B., Bergfeld, W.F., Belsito, D.V., Hill, R.A., Klaassen, C.D., Liebler, D.C., Marks, J.G., Shank, R.C., Slaga, T.J., Snyder, P.W., Andersen, F.A., 2016. Safety Assessment of Alkyl PEG/PPG Ethers as Used in Cosmetics. *Int J Toxicol* 35 (1), 60S–89S. <https://doi.org/10.1177/1091581816650626>.
- [47] Brenz, F., Linke, S., Simat, T.J., 2021. Linear and cyclic oligomers in PET, glycol-modified PET and Tritan™ used for food contact materials. *Food Addit Contam: Part A* 38 (1), 160–179. <https://doi.org/10.1080/19440049.2020.1828626>.
- [48] Tang, C., Gómez Ramos, M.J., Heffernan, A., Kaserzon, S., Rauert, C., Lin, C.-Y., Mueller, J.F., Wang, X., 2023. Evaluation and identification of chemical migrants leached from baby food pouch packaging. *Chemosphere* 340, 139758. <https://doi.org/10.1016/j.chemosphere.2023.139758>.
- [49] Ríos, F., Lechuga, M., Fernández-Arteaga, A., Jurado, E., Fernández-Serrano, M., 2017. Anaerobic digestion of amine-oxide-based surfactants: biodegradation kinetics and inhibitory effects. *Biodegradation* 28 (4), 303–312. <https://doi.org/10.1007/s10532-017-9797-6>.
- [50] Simoneau, C., Valzacchi, S., Morkunas, V., Van den Eede, L., 2011. Comparison of migration from polyethersulphone and polycarbonate baby bottles. *Food Addit Contam: Part A* 1–6. <https://doi.org/10.1080/19440049.2011.604644>.
- [51] Diera, T., Thomsen, A.H., Tisler, S., Karlby, L.T., Christensen, P., Rosshaug, P.S., Albrechtsen, H.J., Christensen, J.H., 2023. A non-target screening study of high-density polyethylene pipes revealed rubber compounds as main contaminant in a drinking water distribution system. *Water Res* 229. <https://doi.org/10.1016/j.watres.2022.119480>.
- [52] Kim, H.S., Lee, K.Y., Jung, J.S., Sin, H.S., Lee, H.G., Jang, D.Y., Lee, S.H., Lim, K.M., Choi, D., 2023. Comparison of migration and cumulative risk assessment of antioxidants, antioxidant degradation products, and other non-intentionally added substances from plastic food contact materials. *Food Packag Shelf Life* 35, 101037. <https://doi.org/10.1016/j.fpsl.2023.101037>.