Occurrence of Phthalates in Bottled Drinks in the Chinese Market and Its Implications for Dietary Exposure

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Abstract: Ubiquitous occurrences of phthalic acid esters (PAEs) or phthalates in a variety of consumer products have been demonstrated. Nevertheless, studies on their occurrence in various types of bottled drinks are limited. In this study, fifteen PAEs were analyzed in six categories of bottled drinks (n = 105) collected from the Chinese market, including mineral water, tea drinks, energy drinks, juice drinks, soft drinks, and beer. Among the 15 PAEs measured, DEHP was the most abundant phthalate with concentrations ranging from below the limit of quantification (LOQ) to 41,000 ng/L at a detection rate (DR) of 96%, followed by DIBP (DR: 88%) and DBP (DR: 84%) with respective concentration ranges of below LOQ to 16,000 and to 4900 ng/L. At least one PAE was detected in each drink sample, and the sum concentrations of 15 PAEs ranged from 770 to 48,043 ng/L (median: 6286 ng/L). Significant differences with respect to both PAE concentrations and composition profiles were observed between different types of bottled drinks. The median sum concentration of 15 PAEs in soft drinks was over five times higher than that detected in mineral water; different from other drink types. Besides DEHP, DBIP, and DBP, a high concentration of BMEP was also detected in a tea drink. The estimated daily dietary intake of phthalates (EDIs) through the consumption of bottled drinks was calculated based on the concentrations measured and the daily ingestion rates of bottled drink items. The EDIs for DMP, DEP, DIBP, DBP, BMEP, DAP, BEEP, BBP, DCP, DHP, BMPP, BEEP, DEHP, DOP, and DNP through the consumption of bottled mineral water (based on mean concentrations) were 0.45, 0.33, 12.5, 3.67, 2.10, 0.06, 0.32, 0.16, 0.10, 0.09, 0.05, 0.81, 112, 0.13, and 0.20 ng/kg-bw/d, respectively, for Chinese adults. Overall, the EDIs for phthalates through the consumption of bottled drinks were below the oral reference doses suggested by the United States Environmental Protection Agency (U.S. EPA).

Keywords: phthalate; dietary intake; DEHP; DBP; DIBP; bottled drink
1. Introduction

Phthalic acid esters (PAEs) or phthalates, primarily used to make polyvinyl chloride (PVC), or vinyl, flexible and pliant, are a group of chemicals made of aryl esters of phthalic acid and alkyl. PAEs are generally used to soften plastics because of their strong performance, durability, and stability [1,2]. These phthalate plasticizers are used in hundreds of products in our homes, hospitals, cars, and businesses, such as vinyl flooring, plastic packaging, toys, medical tubing, and cosmetics [3–7]. For example, Xu et al. (2020) reported the sum concentrations of dimethyl phthalate (DMP), diethyl phthalate (DEP), and dibutyl phthalate (DBP) ranged from 102 to 710 µg/kg in polyethylene terephthalate (PET) bottles collected from Beijing, China [8]. PAEs are not covalently bound to the plastic [9,10], so they can be easily released into the environment, leading to potential human exposure through ingestion, dermal absorption, and inhalation.

As a group of well-studied endocrine-disrupting chemicals, phthalates exposure has been associated with a variety of health effects, including premature thelarche, endometriosis, low semen quality, diabetes, overweight and obesity, allergy and asthma, and reproductive health [11,12]. Diethylhexyl phthalate (DEHP) is one of the most-studied phthalates, and accumulative evidence showed that DEHP exposure was significantly related to insulin resistance and higher systolic blood pressure as well as reproductive system problems [13,14]. Potential toxicity mechanisms of DEHP exposure include the activation of Kupffer’s cells and the nuclear receptor peroxisome proliferator-activated receptor (PPARα) [15–17]. Evidence has shown that phthalates’ toxicity heavily depends on their chemical structures [18]. Based on the difference in carbon backbones in the alkyl side chain, phthalates are differentiated into low and high molecular weight categories. Low molecular weight (LMW) phthalate plasticizers have straight carbon backbones of C3–C6 in the alkyl side chains, while high molecular weight (HMW) phthalate plasticizers have straight C7–C13 carbon backbones in the alkyl side chains [18]. Studies have indicated that LMW phthalates can cause adverse reproductive effects, while HMW phthalates and those C1–C2 backbone alkyl phthalates do not show adverse reproductive effects [18]. The US Environmental Protection Agency (EPA) listed DEHP and butyl benzyl phthalate (BBP) as probable and possible human carcinogens, respectively [11]. European authorities have also classified LMW phthalates with C3–C6 backbone alkyl phthalates as presumed human reproductive toxicants.

Parent phthalates and their metabolites have been detected in a variety of human samples, including serum [19], urine [20,21], semen [22], breast milk [23], and breast tumor tissue [24]. Considerable efforts have also been made to characterize the sources of human exposure to PAEs [25,26], and the ubiquitous occurrence of PAEs in both consumer products [25–28] and environmental matrices [29–31] has been reported. The accumulating evidence has shown that the sources and routes of human exposure to individual PAEs can vary depending on their physicochemical properties [26,31–33]. For example, cosmetics and personal care products are the major sources of human exposure to LMW phthalates [25], diet has been a major source of exposure to HMW phthalates, especially DEHP [31,32,34], and inhalation is the predominant exposure route to DMP [32]. Recent studies have indicated that drinking water is also an important source of human exposure to PAEs. For example, Liu et al. (2015) performed a national survey and risk assessment of phthalates in drinking water from waterworks in China and found that DBP and DEHP were the most abundant PAEs among the six PAEs measured at median levels of 0.18 ± 0.47 and 0.18 ± 0.97 µg/L, respectively [35]. Thuy et al. (2021) surveyed the contamination levels and distribution patterns of ten PAEs in various types of water samples, including bottled water and tap water, collected from Hanoi, Vietnam, and suggested widespread occurrence of PAEs in the water samples [36]. However, little is known of the occurrence of phthalates in bottled drinks commercially available in the market, although the consumption of bottled drinks is huge.

This study aims to investigate the occurrence and distribution levels of fifteen typical phthalates in 105 popular branded bottled drinks in the Chinese market, including mineral
water ($n = 19$), a tea drink ($n = 22$), an energy drink ($n = 15$), a juice drink ($n = 15$), a soft drink ($n = 25$), and beer ($n = 9$), in order to estimate human exposure to phthalates through the consumption of bottled drinks. We also chemometrically investigate if grouping and correlations among PAEs and bottled drinks from the Chinese market exist. To our knowledge, this is the first survey on phthalates in various types of bottled drinks collected from the Chinese market.

2. Materials and Methods

2.1. Standards and Reagents

Fifteen phthalates, including dimethyl phthalate (DMP), diethyl phthalate (DEP), dibutyl phthalate (DBP), dinonyl phthalate (DNP), diamyl phthalate (DAP), dihexyl phthalate (DHP), diisobutyl phthalate (DIBP), butyl benzyl phthalate (BBP), bis(2-Ethoxyethyl) phthalate (BEEP), bis(2-methoxyethyl) phthalate (BMEP), bis(2-n-Butoxyethyl) phthalate (BBEIP), bis(4-Methyl-2-penty1) phthalate (BMPP), dioctyl phthalate (DOP), dicyclohexyl phthalate (DCP), and diethylhexyl phthalate (DEHP), were analyzed in this study. Detailed information regarding the 15 PAEs is shown in Table S1. Nine deuterated internal standards, including $d_4$-DMP, $d_4$-DEP, $d_4$-DBP, $d_4$-DNP, $d_4$-DHP, $d_4$-DIBP, $d_4$-DOP, $d_4$-DCP, and $d_4$-DEHP, were used as surrogate standards in the quantification of phthalates. Both the target and surrogate standards were purchased from AccuStandard, Inc. (New Haven, CT, USA), with a purity of >99%. Analytical-grade acetone and acetonitrile were purchased from Macron Chemicals (Nashville, TN, USA), and hexane and HPLC-grade water were purchased from J. T. Baker (Phillipsburg, NJ, USA).

2.2. Sample Collection and Analysis

A total of 105 bottled drinks were collected from local supermarkets in Dalian, Liaoning Province, China, including mineral water ($n = 19$), a tea drink ($n = 22$), an energy drink ($n = 15$), a juice drink ($n = 15$), a soft drink ($n = 25$), and beer ($n = 9$). The drink samples collected in this study were popular brands that were consumed widely by the Chinese population.

All the drink samples were spiked with surrogate standards prior to extraction, following the extraction protocol described earlier [28]. In brief, 200 ng of each surrogate standard was spiked into 1500 mL of the bottled drink sample. Spiked samples were thoroughly mixed for 5 min and allowed to equilibrate at room temperature for 30 min. Then 10 mL hexane was used for extraction via shaking in a mechanical shaker at 250 oscillations/min for 30 min. After centrifugation, the hexane layer was transferred into a clean glass flask. The extraction was repeated three times, and the hexane extract was combined and concentrated using a rotary evaporator to 1 mL and transferred into a gas chromatography (GC) vial for analysis.

The instrumental analysis protocol of phthalates was described elsewhere in earlier studies [28,31]. Briefly, the analysis was performed using GC (Agilent Technologies 6890, Santa Clara, CA, USA) coupled with mass spectrometry (Agilent Technologies 5973, Santa Clara, CA, USA) in the selection ion monitoring (SIM) mode. The chromatography separation was carried out using a fused silica capillary column (DB-5 ms, 30 m × 0.25 mm × 0.25 μm; Agilent Technologies; Santa Clara, CA, USA). The detailed parameters for the GC-MS condition for PAE analysis are shown in Table S2.

2.3. Quality Assurance/Quality Control

Prior to the analysis of samples, considerable effort was made to reduce the background contamination from the analytical procedures following the earlier studies [7]. Briefly, all glassware was washed with a detergent and Milli-Q water, followed by solvents (i.e., acetone and hexane), baked at 450 °C for overnight, and kept in an oven at 100 °C until use. All solvents were tested for background levels of phthalates and the batches of solvents that contained the lowest levels of phthalates were used throughout the analysis. Prior to each batch of analysis, pure hexane was injected into GC–MS until the background
level was stable. Within each batch of ten samples, three solvent blanks and three procedural blanks and a pair of matrix-spike samples were processed together. Trace levels of phthalates found in procedural blanks were subtracted from the measured concentrations in bottled drink samples (Table S2). The quantification of phthalates in the samples was based on the isotope dilution method. The calibration curves were prepared by plotting a concentration – response factor for each target analyte (peak area of analyte divided by peak area of the internal standard) versus the response-dependent concentration factor (the concentration of the analyte divided by the concentration of the internal standard). The regression coefficients (r) were ≥ 0.99 for all calibration curves. The limits of quantification (LOQs) were calculated based on the instrument detection limits (a quantifiable peak must have a signal-to-noise ratio > 10, and a dilution factor in sample preparation (Table S3)). Recoveries of surrogate standards were calculated using matrix spikes of both low (50 ng each PAE) and high (500 ng each PAE) amounts of chemical spikes, and the recoveries ranged from 82% to 113% (Table S3). The relative standard deviation (RSD) was calculated by analyzing a high amount of matrix spike replicates (n = 3) to evaluate the reproducibility and repeatability of the analysis, and the RSDs of PAEs are below 10% (Table S3).

2.4. Statistical Analysis

Basic descriptive statistical analysis was performed using Microsoft Excel (Microsoft Office 2013). For concentrations below the LOQs, a value of half the LOQ was used in the calculation [37,38]. As a major tool for simplifying the large initial datasets, principal component analysis (PCA) has been widely used in the investigation of possible sources of chemical pollutants in the environment [38,39]. Here, Euclidean distance-based constrained analysis of principal coordinates (CAP), a type of principal component analysis, was used to provide information regarding the sources of PAEs in the analyzed bottled drink samples, and to compare the PAEs concentrations among different groups [40]. PRIMER-e (version 7, PRIMER-E, Ivybridge, UK) with PERMANOVA+ add-on software (PRIMER-E Ltd., Ivybridge, UK) was used in the PCA analysis, and the statistical significance level was set at α < 0.05.

2.5. Exposure Doses and Health Risk Assessment of PAEs through Consumption of Bottled Drinks

Daily intake of phthalates through the consumption of bottled drinks by the Chinese population was estimated via the following equation [31]:

\[
EDI_{\text{drink}} = \frac{CQ}{bw} \quad (1)
\]

where \( EDI_{\text{drink}} \) (ng/kg-bw/d) is the estimated daily intake from drink, \( C \) (ng/g) is the phthalate concentration in the drink, \( Q \) (g/day) is the average amount of daily intake of the drink, and \( bw \) (kg) is body weight. For Chinese adults, 60 kg and 2000 g/day were used as the \( bw \) and \( Q \) values, respectively.

Both carcinogenic and non-carcinogenic risks of the select PAEs through the consumption of bottled drinks were assessed following the methods described earlier [41]. The selection of PAEs was based on the availability of relevant parameters in the Integrated Risk Information System, prepared and maintained by the U.S. Environmental Protection Agency (U.S. EPA) [42]. The carcinogenic risk (R) from exposure to PAEs via the consumption of bottled drinks was calculated by the following equation:

\[
R = SF \times EDI \quad (R < 0.01) \quad (2)
\]

\[
R = 1 - \exp(-EDI \times SF) \quad (R \geq 0.01) \quad (3)
\]

where \( SF \) is the carcinogenic slope factor of oral intake. The \( SF \) value for DEHP is 0.014 (Kg d)/mg [42].
The hazard index (HI) was used to assess non-cancer risks, calculated using the following equation:

$$HI = \frac{EDI}{RfD}$$

where $RfD$ is the reference dose for the non-carcinogenic health risk of a chemical proposed by the guidelines. The $RfD$ of BBP, DBP, DEP, and DEHP is 0.2, 0.1, 0.8, and 0.02 mg/Kg/d, respectively [42]. HI below 1 indicates safety concerns [41].

### 3. Results and Discussion

#### 3.1. Concentrations of Phthalates in Bottled Drinks

Overall, at least one PAE was detected in each one of the 105 bottled drinks analyzed (Table 1). The sum concentrations of 15 PAEs measured in the 105 bottled drink samples ranged from 770 to 48,004 ng/L at a median level of 6286 ng/L (Table 1). Among the 15 PAEs measured in this study, DEHP was the predominant compound detected in the bottled drinks (detection rate, DR: 96%; median: 2000 ng/L; range: <LOQ-41000 ng/L), followed by DIBP (88%; 2100; <LOQ-16000) and DBP (84%; 820; <LOQ-4900) (Table 1). All other PAEs were also frequently detected in this study with DRs over 59%, but their contributions to the sum mean concentration of the 15 PAEs were low, with a contribution ratio between 0.1% and 4.4% (Table 1).

| Chemical | DR (%) | Mean (ng/L) | SD (ng/L) | GM (ng/L) | Median (ng/L) | Range (ng/L) | Ratio (%) |
|----------|--------|-------------|-----------|-----------|---------------|--------------|-----------|
| DMP 75.2 | 277    | 837         | 64.9      | 65        | <LOQ–7300     | 3.0          |
| DEP 59.0 | 32.9   | 44.2        | 20.3      | 17        | <LOQ–390      | 0.4          |
| DIBP 87.6 | 2825   | 2796        | 1491      | 2100      | <LOQ–16000    | 30.7         |
| DBP 83.8 | 1097   | 1119        | 551       | 820       | <LOQ–4900     | 11.9         |
| BMPE 87.6 | 404    | 2074        | 36.5      | 39        | <LOQ–17000    | 4.4          |
| DAP 61.0 | 41.0   | 174         | 5.12      | 3.5       | <LOQ–1400     | 0.5          |
| BEEP 84.8 | 63.4   | 61.2        | 32.8      | 50        | <LOQ–270      | 0.7          |
| BBP 81.9 | 97.6   | 464         | 13.3      | 12        | <LOQ–3800     | 1.1          |
| DCP 76.2 | 14.6   | 15.8        | 9.4       | 9.5       | <LOQ–110      | 0.2          |
| DHP 60.0 | 6.88   | 8.46        | 4.16      | 3.7       | <LOQ–51       | 0.1          |
| BMPP 75.2 | 16.4   | 39.2        | 6.6       | 6.2       | <LOQ–280      | 0.2          |
| BBEPP 87.6 | 92.0   | 111         | 48.4      | 61        | <LOQ–760      | 1.0          |
| DEHP 96.2 | 4193   | 6949        | 2025      | 2000      | <LOQ–41000    | 45.5         |
| DOP 78.1 | 10.6   | 13.0        | 6.28      | 7         | <LOQ–86.0     | 0.1          |
| DNP 81.0 | 35.9   | 137         | 9.45      | 9.8       | <LOQ–1300     | 0.4          |
| (sum) 100 | 9207   | 8952        | 6127      | 6286      | 770–8004      |             |

*a*: DR detection rate; *b*: SD, standard deviation; *c*: GM, geometric mean; *d*: ratio, concentration ratio (%), calculated as the ratio between the mean concentration of each target analyte versus the mean sum concentration of 15 PAEs; *e*: LOQ, limit of quantification.

Mineral water is the most commonly used bottled drink among the Chinese population. Among the 15 PAEs measured, DEHP was the most frequently detected and most-abundant chemical in the mineral water samples, with a DR of 100% and median concentration of 1600 (range: 500–15,000) ng/L, followed by DIBP (DR: 58%; median: 170; range: <LOQ-940) and DBP (37%; 57.0; <LOQ-320) (Tables 2 and 3). The distribution pattern is similar to that observed when taking other types of bottled drinks into account (Table 1), but different from what was observed in bottled waters collected from other countries such as Vietnam [36]. Differences in packaging material, water source, and other materials used in the production and bottling between the two countries may explain this observation. When compared with the concentration in bottled water or tap water samples collected from other regions, the concentration of DEHP in mineral water was at a higher level (at the same level as that calculated when taking other types of drinks into account), but the concentrations of DIBP and DBP were at lower levels (DIBP and DBP levels were also at higher levels when taking other types of bottled drinks into account), as shown in Table 2. This indicates that bottled mineral water/drinks are an important source of
human exposure to DEHP, similar to other dietary sources such as foodstuffs [28]. The sum concentrations of 15 PAEs measured in 19 bottled mineral water samples ranged from 770 to 16,301 ng/L (median: 1805 ng/L) (Table 3). Median individual PAE concentrations in the bottled drink samples (n = 105) were 1.3–16.1 times higher than that detected in the bottled mineral water samples (n = 19) (Tables 1 and 3).

Table 2. Concentration\(^a\) (ng/L) comparison of DEHP, DIBP, DBP, and BMEP in bottled drink, bottled water, and tap water samples from various studies.

| Sample Type          | Location       | n     | DEHP            | DIBP            | DBP             | BMEP            | Reference                        |
|----------------------|----------------|-------|-----------------|-----------------|-----------------|-----------------|----------------------------------|
| mineral water        | Dalian, China  | 19    | 3351 (500–15000) | 375 (<LOQ\(^b\)-940) | 110 (<LOQ-320) | 63 (<LOQ-310) | this study                       |
| tea drink            | Dalian, China  | 22    | 2660 (500–12000) | 3770 (<LOQ-9900) | 1197 (<LOQ-3600) | 630 (1701–17000) | this study                       |
| energy drink         | Dalian, China  | 15    | 4738 (<LOQ-34000) | 1539 (<LOQ-4300) | 630 (1701–17000) | 63 (<LOQ-220) | this study                       |
| juice drink          | Dalian, China  | 15    | 3682 (440–27000) | 4521 (<LOQ-4300) | 2363 (290–4900) | 73 (8.9–190) | this study                       |
| soft drink           | Dalian, China  | 25    | 7198 (<LOQ-41000) | 3916 (1000–7200) | 1290 (93–3000) | 56 (<LOQ-330) | this study                       |
| beer                 | Dalian, China  | 9     | 1317 (440–3700) | 1974 (<LOQ-34000) | 1064 (210–3000) | 37 (<LOQ-130) | this study                       |
| total                | Dalian, China  | 105   | 4193 (<LOQ-41000) | 2825 (<LOQ-16000) | 1097 (<LOQ-4900) | 404 (<LOQ-17000) | this study                       |
| non-carbonated water | Hanoi, Vietnam | 11    | 873 (227–1950) | 1100 (94.0–3930) | 1150 (145–3070) | -                | Le et al. (2021) [36]            |
| carbonated water     | Hanoi, Vietnam | 10    | 1120 (103–2710) | 1790 (123–5190) | 1740 (93.0–4710) | -                | Le et al. (2021) [36]            |
| carbonated soft drinks | Tehran, Iran  | 4     | 8423 (6767–14008) | -                | -                | -                | Moazzen et al. (2018) [43]       |
| bottled water        | Tianjin, China | 6     | 1074 (880–1257) | -                | 486 (465–517) | -                | Wang et al. (2021) [41]          |
| bottled water        | 21 global countries | 367–379 | 3420 (nd\(^c\)-9410) | - | 5350 (nd-2220) | - | Luo et al. (2018) [44]          |
| bottled water        | Tehran, Iran   | 10    | 100 (70–120) | 959 (100–1890) | 1574 (60–6500) | -                | Abtahi et al. (2019) [45]        |
| bottled water        | Portugal        | 7     | 100 (20–180) | 959 (100–1890) | 1574 (60–6500) | -                | Santana et al. (2013) [46]       |
| tap water            | Tehran, Iran   | 40    | 150 (nd-380) | -                | 90 (nd-140) | -                | Abtahi et al. (2019) [45]        |
| tap water            | Hanoi, Vietnam | 7     | 5340 (1010–14500) | 456 (27.0–1390) | 796 (14.0–2560) | -                | Le et al. (2021) [36]            |
| tap water            | China           | 225   | 770 (<LOQ-5510) | -                | 350 (<LOQ-1560) | -                | Liu et al. (2015) [35]           |
| tap water            | Tianjin, China | 6     | 1338 (1097–1780) | -                | 541 (380–679) | -                | Wang et al. (2021) [41]          |

\(^a\): mean concentration and the concentration range were used in this Table; \(^b\): LOQ, limit of quantification; \(^c\): nd, non-detected.

Concentrations of PAEs in both bottled mineral water samples and bottled drink samples analyzed in this study were at higher levels compared with those reported in other countries, e.g., Iran [43,45] and Portugal [46]. This may be partly ascribed to the fact that more types of phthalates (15 vs. 6 [43], 6 [45], and 11 [46], respectively) were measured in this study as well as the differences in the sample pretreatment method, analytical technique, data analysis method, etc. Le et al. (2021) [36] recently reported the concentrations of 10 typical PAEs in bottled water collected from Hanoi, Vietnam with the mean concentration being 6400 (range: 1640–15,700) ng/L, which is higher than that detected in mineral water yet lower than that in bottled drinks analyzed in this study. The
PAE concentrations in the bottled drinks detected in this study are lower than that reported by Luo et al. (2018) [44] in bottled waters from 21 countries (mean: 14,900 ng/L; range: n.a.–200,000 ng/L).

### Table 3. Concentrations (ng/L) of phthalates in different types of bottled drinks.

| DMP | DEP | DBP | MBEAP | BEEP | BBEAP | DCP | DMP | BBEP | DEHP | DOB | DNP | Σ(sum) |
|-----|-----|-----|-------|------|-------|-----|-----|------|------|-----|-----|--------|
| DR<sub>a</sub> | 26  | 5   | 58   | 37   | 53   | 5   | 4   | 21   | 11   | 5   | 53   | 100   | 47   | 53   | 100   |
| mean | 13.7 | 9.8 | 375  | 110  | 62.9 | 1.8 | 9.5 | 4.9  | 3.1  | 2.6 | 1.5  | 24.2  | 3351 | 3.8  | 5.9  | 3980  |
| SG<sup>b</sup> | 6.7 | 7.8 | 337  | 80.8 | 103  | 1   | 20.9 | 8.7  | 1.0  | 4.0 | 0.2  | 51.2  | 4321  | 3.0  | 5.4  | 4637  |
| GM<sup>c</sup> | 12.6 | 8.7 | 2631 | 89.3 | 13.7 | 1.7 | 2.9  | 3.0  | 0.9  | 2.9 | 3.2  | 10.9  | 1889  | 7.0  | 1.8  | 8754  |
| median | 10.0 | 8.0 | 170  | 57.0 | 7.0  | 1.6 | 3.1  | 1.9  | 2.6  | 1.6 | 1.5  | 6.5   | 1600  | 1.6  | 4.4  | 1805  |
| range | <LOQ<sup>d</sup> | <LOQ<sup>d</sup> | 450  | 250  | <LOQ<sup>d</sup> | <LOQ<sup>d</sup> | <LOQ<sup>d</sup> | <LOQ<sup>d</sup> | 520  | 190 | 230  | 230   | 15000 | 12.0 | 19.0 | 16301 |
| ratio<sup>d</sup> | 0.3 | 0.3 | 9.4  | 2.8  | 1.6  | 0.1 | 0.1  | 0.1  | 0.1  | 0.04 | 0.6  | 84.2  | 0.1   | 0.2  | 0.2   |

<sup>a</sup> DR, detection rate (%); <sup>b</sup> SD, standard deviation (ng/L); <sup>c</sup> GM, geometric mean (ng/L); <sup>d</sup> ratio, concentration ratio (%), calculated as the ratio between the mean concentration of each target analyte versus the mean sum concentration of 15 PAEs; <sup>e</sup> LOQ, limit of quantification.

Several studies also investigated the concentrations of PAEs in bottled water samples in China, but the reported concentrations are lower than those found in mineral water in this study. Liu et al. (2015) collected a total of 225 drinking water samples from the waterworks in different regions of China and determined the concentrations of six typical PAEs including DEP, DMB, DBP, BBP, DEHP, and DOP, and the mean sum concentration was 1278 ng/L [35] (mean concentration was 4015 ng/L for mineral water samples in this study). Wang et al. (2021) collected bottled water samples from Tianjin, China, and reported that the mean sum concentration of DBP, BBP, and DEHP was 1960 ng/L [41]. Li et al. (2019) reported the concentrations of seven PAEs (DMP, DEP, DMB, DBP, BzBP,
DEHP, and DnOP) in 60 bottled water samples collected in Beijing, China, and the sum PAE concentrations ranged from 155 to 5200 (mean: 519) ng/L [47].

Overall, the concentration of individual PAE in bottled drinks did not exceed the maximum contaminant levels recommended by national and international authorities (e.g., in China, the guideline values for DEHP, DBP, and DEP are 8, 3, and 300 µg/L, respectively [48]; the guideline value for DEHP in WHO [49] and the U.S. [50] are 8 and 6 µg/L, respectively). However, the concentration of individual PAE in select bottled drinks may exceed the no-observed-adverse-effect level (NOAEL) suggested by U.S. EPA (e.g., NOAELs for BBP and DEHP in water are 0.10 and 0.32 µg/L, respectively [51]). We further calculated the hazard index (HI) for DEHP using the highest concentration of DEHP (41000 ng/L) observed in this study. The results showed that the highest HI of DEHP is 0.07, far less than 1, indicating that DEHP in bottled drinks posed negligible non-carcinogenic health risks to human health by ingestion. However, this still warrants attention when performing health risk assessment of chemical exposure because individuals are exposed to thousands of chemicals simultaneously and they may work synergistically in posing risks to human health.

3.2. Factors Influencing Phthalates Concentrations in Bottled Drinks

The bottled drinks analyzed in this study were grouped into six different types of bottled drinks, including (1) mineral water, (2) tea drink, (3) energy drink, (4) juice drink, (5) soft drink, and (6) beer. Compared with other types of drinks, mineral water samples contain the least phthalates with respect to both DRs and concentrations. Of the 15 PAEs measured in this study, only DEHP was detected in over 60% of mineral water samples (DR: 100%); however, in tea drink, energy drink, juice drink, soft drink, and beer samples, the number of PAEs with DRs over 60% was 14, 14, 15, 14, and 14, respectively (Table 3). With respect to concentrations of PAEs, of the six types of bottled drinks, soft drink had the highest sum concentration of 15 PAEs (range: 1991–48,004 ng/L; median: 10,534 ng/L), followed by juice drink (1635–46,541; 10,179), tea drink (1277–27,298; 8459), beer (1895–9104; 4111), energy drink (1184–36,505; 3972), and mineral water (770–16,301; 1805) (Table 3). The median sum concentration of 15 PAEs detected in soft drink samples is over five times higher than that detected in mineral water samples. Thus, considerable differences between the concentrations of PAEs in different types of bottled drinks were observed in this study. This is the first study showing that drink type can significantly impact the concentrations of PAEs in bottled drinks.

To investigate the contribution of each phthalate to the total phthalate burden, we calculated the ratio of the mean concentration of each phthalate to the mean sum concentration of 15 PAEs (Table 3; Figure 1a). As shown in Table 3, DEHP, DBIP, and DBP are the three major PAEs detected in beer, soft drink, juice drink, and energy drink samples, with a contribution ratio of over 10% (or around 10%). The predominant compounds found in the four types of bottled drinks are DIBP, DEHP, DBIP, and DEHP, respectively, with the respective contribution ratios being 41.7%, 53.8%, 37.5%, and 62.1%. In mineral water samples, DEHP is the predominant PAE with a contribution ratio of 84%, followed by DBIP (ratio: 9.4%), and the contribution of DBP is minor (2.8%). In tea drink samples, besides DEHP, DBIP, and DBP, we also observed a significant contribution of BMEP to the sum PAE concentration with a contribution ratio of 17.1% (Tables 2 and 3). This indicates that tea drink is an important source of human exposure to BMEP.
Figure 1. Compositions of total phthalates in different categories of bottled drinks: (a) Sorted by bottled drink types; (b) sorted by packaging material of bottled drinks.

We further examined the concentrations of PAEs in bottled drinks based on the packaging material, including plastic ($n = 56$), glass ($n = 19$), metal ($n = 22$), and paper ($n = 8$) (Table 4; Figure 1b). As shown in Table 4, of the 15 PAEs measured, the majority of chemicals (12–14) had DRs over 60% in each category. DEHP, DBIP, and DBP are the predominant phthalates found in each category with corresponding contribution ratios of over 10%. Compared with other packaging materials, paper-bottled drinks have a higher concentration of BMEP with a contribution ratio of 10.2%. The highest sum concentration of the 15 PAEs was found in paper-bottled drinks (range: 6418–46,541 ng/L; median: 11,119 ng/L), followed by glass-bottled drinks (1635–23,256; 10,190), metal-bottled drinks (3078–8,004; 7501), and plastic-bottled drinks (770–27,298; 4340). This is different from our assumption that plastic may contain higher amounts of PAEs, which might be explained by the following reasons. Firstly, the sample size not large enough to investigate the impact of packaging material on PAEs concentrations within the same drink type. Secondly, even within the same type of packaging material, various sub-types exist. For example, different vendors may use different types of plastic in bottling the drinks. PAE concentrations may vary significantly depending on the specific plastic employed.

Table 4. Concentrations (ng/L) of phthalates in bottled drinks sorted by the packaging material.

|        | DMP | DEP | DIBP | DBP | BMEP | DAP | BEEP | BBP | DCP | DHP | BMPP | BBEP | DEHP | DOP | DNP | ∑(sum) |
|--------|-----|-----|------|-----|------|-----|------|-----|-----|-----|------|------|------|-----|-----|--------|
| DR     | 73  | 57  | 77   | 70  | 82   | 59  | 75   | 75  | 71  | 59  | 64   | 84   | 84   | 71  | 71  | 100    |
| mean   | 217 | 33.7| 1968 | 920 | 708  | 14.9| 54.3 | 36.3| 17.0| 7.7 | 13.1 | 112  | 2826 | 12.8| 24.9| 6964   |
| GMF    | 53.7| 19.6| 861  | 336 | 44.1 | 4.6 | 25.2 | 10.5| 10.2| 4.5 | 57   | 54.0 | 167  | 6.6 | 10.0| 4559   |
| median | 45.0| 17.0| 1100 | 280 | 49.5 | 3.3 | 51.5 | 9.8 | 11.0| 5.2 | 5.5  | 76.5 | 1650 | 7.4 | 11.0| 4340   |
| range  | <LOQ |<LOQ |<LOQ |<LOQ|<LOQ   |<LOQ|<LOQ |<LOQ|<LOQ|<LOQ |<LOQ |<LOQ |<LOQ |<LOQ |<LOQ |<LOQ   |
| rat    | 3.1 | 0.5 | 28.3 | 13.2| 10.2 | 0.2 | 0.8  | 0.5 | 0.2 | 0.1 | 0.2  | 1.6  | 40.6 | 0.2 | 0.4|       |

|        | DMP | DEP | DIBP | DBP | BMEP | DAP | BEEP | BBP | DCP | DHP | BMPP | BBEP | DEHP | DOP | DNP | ∑(sum) |
|--------|-----|-----|------|-----|------|-----|------|-----|-----|-----|------|------|------|-----|-----|--------|
| DR     | 79  | 53  | 100  | 100 | 95   | 63  | 90   | 84  | 79  | 68  | 79   | 90   | 90   | 100 | 74  | 79    |
| mean   | 524 | 28.8| 3510 | 1285| 63.0 | 5.6 | 56.3 | 222 | 8.4 | 7.2 | 20.7 | 42.3 | 6083 | 5.4 | 10.2| 11,871 |
| SD     | 1653| 26.4| 3740 | 1042| 75.9 | 5.9 | 75.7 | 867 | 5.7 | 11.2| 55.9 | 31.5 | 9060 | 3.8 | 9.0 | 9584   |
| GM     | 94.3| 18.8| 2085 | 853 | 33.1 | 3.9 | 29.4 | 15.9| 6.8 | 4.2 | 6.7  | 28.9 | 2915 | 4.2 | 6.7 | 8418   |
| median | 109 | 12.0| 2600 | 840 | 43.0 | 3.4 | 28.0 | 10.0| 6.2 | 3.7 | 6.2  | 32.0 | 2600 | 4.1 | 8.4 | 10,190 |
| range  | <LOQ |<LOQ |<LOQ |<LOQ|<LOQ   |<LOQ|<LOQ |<LOQ|<LOQ|<LOQ |<LOQ |<LOQ |<LOQ |<LOQ |<LOQ |<LOQ   |
| ratio  | 4.4 | 0.2 | 29.6 | 10.8| 0.5  | 0.1 | 0.5  | 1.9 | 0.1 | 0.1 | 0.2  | 0.4  | 51.2 | 0.1 | 0.1|       |
3.3. Principal Component Analysis (PCA) of Phthalates in Bottled Drinks

PCA was applied to provide information regarding the possible sources of PAEs detected in the bottled drink samples in Dalian, China. Here, we performed a canonical analysis of the principal coordinates (CAP) method to analyze the input dataset after log-transformation and standardization. CAP allows a constrained ordination to be done on the basis of any distance or dissimilarity measure. The analytical results on PAEs present in 105 bottled drink samples showed that the top six principal components, abbreviated as CAP here, explained 78.3% of the total variance in the data, with the top two CAPs explaining 37.3% and 11.0% variance, respectively. The percentages of the total variance explained by other CAPs are all below 10%. This indicates that there is only one major source of PAEs present in the bottled drinks, and a variety of factors are contributing to the PAEs concentrations in the bottled drinks analyzed in this study.

The correlation coefficients between the new abstract principal components and the PAEs were also provided, indicating how well the new abstract principal components correlate with the PAEs (Table S4). The first new abstract principal component, CAP1, correlates positively with all the PAEs measured in this study, implying that higher concentrations of PAEs were linked to higher values of CAP1. This could be explained by the same exposure sources of PAEs present in these bottled drinks. Permutational multivariate analysis of variance was carried out to compare PAEs concentrations among different types of drinks, and a significant difference ($p < 0.001$) was observed, especially between mineral water and other types of drinks, as shown in Figure 2a. In addition, results of permutational multivariate analysis of variance also indicated the significant difference ($p < 0.001$) of the PAE concentrations among bottled drinks with different packaging materials (Figure 2b). Thus, both drink type and packaging material are associated with the PAEs (Table S4). The first new abstract principal component, CAP1, correlates with the PAEs concentrations in the bottled drinks analyzed in this study.

Permutational multivariate analysis of variance was carried out to compare PAEs concentrations among different types of drinks, and a significant difference ($p < 0.001$) was observed, especially between mineral water and other types of drinks, as shown in Figure 2a. In addition, results of permutational multivariate analysis of variance also indicated the significant difference ($p < 0.001$) of the PAE concentrations among bottled drinks with different packaging materials (Figure 2b). Thus, both drink type and packaging material are associated with the PAEs in the samples. This further corroborated the earlier conclusion that many factors contribute to the PAEs present in the bottled drinks.

3.4. Dietary Exposure to PAEs through Consumption of Bottled Drinks in China

The human exposure doses of 15 PAEs through the ingestion of bottled drinks were estimated based on the mean/maximum concentrations of PAEs measured in different types of bottled drinks, as shown in Table 5. The average daily intake of drink for Chinese adults was estimated as 1 L per day [41]. Mineral water is the most commonly used bottled drink among the Chinese population. Among PAEs, the mean exposure doses of DEHP were the highest from the consumption of mineral water (mean/maximum dose: 112/500 ng/kg-bw/d), followed by DBP (12.5/31.3) and DMP (3.67/10.7). The mean/maximum human exposure doses from mineral water for other PAEs (DMP, DEP, BMEP, DAP, BEEP, BBP, DCP, DHP, BMPP, BBEP, DEHP, DOP, and DNP) were 0.45/1.03, 0.33/1.40, 0.45/1.03, 0.33/1.40, 0.45/1.03, 0.33/1.40, 0.45/1.03, 0.33/1.40, 0.45/1.03, 0.33/1.40, 0.45/1.03, 0.33/1.40.
2.10/10.3, 0.06/0.20, 0.32/3.17, 0.16/1.33, 0.10/0.19, 0.09/0.63, 0.05/0.08, 0.81/7.67, 0.13/0.40, and 0.20/0.63 ng/kg-bw/d, respectively. The mean/maximum human exposure doses to the total phthalates were 133/544 ng/kg-bw/d.

Figure 2. Plots of the canonical analysis of principal (CAP) of PAEs among different types of bottled drinks (a) and bottled drinks with different packaging materials (b). Permutational multivariate analysis of variance results are also shown in the figure.

Table 5. Estimated daily intake (EDI\textsubscript{drink}, ng/kg-bw/d) of PAEs through ingestion of bottled drinks, based on mean/maximum concentrations.

| Chemical | Mineral Water | Energy Drink | Beer | Tea Drink | Juice Drink | Soft Drink |
|----------|---------------|--------------|------|-----------|-------------|------------|
| DMP      | 0.45/1.03     | 7.72/36.7    | 3.77/9.67 | 5.91/43.3 | 27.3/243 | 10.9/103 |
| DEP      | 0.33/1.40     | 0.92/3.27    | 1.19/2.43 | 1.27/3.67 | 1.27/2.90 | 1.49/13.0 |
| DIBP     | 12.5/31.3     | 513/143      | 65.8/137 | 126/330   | 151/533   | 131/240   |
| DBP      | 3.67/10.7     | 21.0/96.7    | 35.5/100 | 39.9/120  | 78.8/163  | 43.0/100  |
| BMEP     | 2.10/10.3     | 2.11/7.33    | 1.23/4.33 | 56.7/567  | 2.43/6.33 | 1.860/11.0 |
| DAP      | 0.06/0.20     | 0.46/5.00    | 0.18/0.47 | 0.42/3.33 | 6.75/46.7 | 0.93/10.3 |
| BEEP     | 0.32/3.17     | 3.16/9.00    | 2.03/4.33 | 1.78/5.00 | 3.82/8.00 | 2.14/7.33 |
| BBP      | 0.16/1.33     | 2.69/28.3    | 0.44/1.20 | 0.89/6.33 | 1.72/13.7 | 9.95/127  |
| DCP      | 0.10/0.19     | 0.64/1.23    | 0.27/0.53 | 0.75/3.67 | 0.54/2.07 | 0.50/2.37 |
| DHP      | 0.09/0.63     | 0.35/0.67    | 0.16/0.33 | 0.25/1.63 | 0.31/0.80 | 0.23/1.70 |
| BMPP     | 0.05/0.08     | 0.46/1.23    | 0.28/0.80 | 0.42/1.83 | 0.56/1.23 | 1.17/9.33 |
| BBEP     | 0.81/7.67     | 4.66/8.33    | 2.80/11.0 | 4.76/25.5 | 2.95/7.33 | 2.48/7.00 |
| DEHP     | 112/500       | 158/1133     | 43.9/123 | 88.7/400  | 123/900   | 240/1367  |
| DOP      | 0.13/0.40     | 0.58/2.10    | 0.20/0.57 | 0.53/2.87 | 0.34/1.07 | 0.29/1.00 |
| DNP      | 0.20/0.63     | 0.34/1.77    | 0.28/0.67 | 3.49/43.3 | 1.63/16.7 | 0.52/1.73 |
| Σ(sum)   | 133/544       | 254/1217     | 158/304 | 331/910   | 402/1551  | 446/1600  |

Of the six types of bottled drinks analyzed, the highest mean exposure doses of DEHP (240/1367), DIBP (151/533), and DBP (78.8/163) can be obtained through the consumption of soft drinks, juice drinks, and juice drinks, respectively. Other high exposure doses of individual PAEs include DMP though juice drinks (27.3/243) and BMEP through tea drinks (56.7/567). Based on the highest mean exposure doses of each PAE, it can be generalized that the EDI\textsubscript{drink} values were in the order of 0.10 ng/kg-bw/d for DCP, DHP, BMPP, and
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DOP, 1.00 ng/kg-bw/d for DAP, BBP, DNP, DMP, DEP, BEEP, and BBEP, 10.0 ng/kg-bw/d for BMEP and DBP, and 100 ng/kg-bw/d for DIBP and DEHP.

Human exposure doses of PAEs through the consumption of bottled drinks were several orders of magnitude lower than the oral reference doses suggested by the U.S. FDA (20, 100, 200, and 800 µg/kg-bw/d for DEHP, DBP, BBP, and DEP, respectively) [52], even when the highest phthalate concentrations in bottled drinks were used in the estimation. However, humans are exposed to PAEs via multiple pathways including inhalation, diet ingestion, and dermal absorption. The evidence has shown that dietary exposures represent a small fraction of the total exposure doses (e.g., contributed ~10% for DBP, ~10% for DMP, and ~2% for DEP to the total exposures) [28]. Other exposure sources such as personal care products also play crucial roles in human exposure to phthalates. Thus, it is highly likely that the entire human exposure doses to phthalates for individuals might exceed the oral reference doses recommended by the U.S. FDA.

3.5. Health Risk Assessment of Select PAEs through Consumption of Bottled Drinks in China

Human cancer risk caused by DEHP via consumption of different types of bottled drinks was assessed by calculating the carcinogenic risk (R). Based on the mean concentrations of DEHP detected in different types of bottled drinks, the cancer risks of DEHP for mineral water, tea drink, energy drink, juice drink, soft drink, and beer are $1.6 \times 10^{-6}$, $1.2 \times 10^{-6}$, $2.2 \times 10^{-6}$, $1.7 \times 10^{-6}$, $3.4 \times 10^{-6}$, and $0.6 \times 10^{-6}$, respectively. Except for beer, the cancer risks of DEHP for other types of bottled drinks are higher than the maximum acceptable risk level, which is $1.0 \times 10^{-6}$ [38]. Thus, the potential carcinogenic risk attributable to DEHP present in the bottled drink samples should be of concern for Chinese consumers. Consumption of bottled drinks over a long duration could be harmful to human health.

Non-carcinogenic risks of DEHP, DBP, DEP, and BBP were also evaluated via the calculation of HIs. The results showed that mean HIs for DEHP, DBP, DEP, and BBP were $5.6 \times 10^{-3}$, $3.7 \times 10^{-5}$, $0.4 \times 10^{-6}$, and $0.8 \times 10^{-6}$, respectively. These values are far less than 1, indicating that these PAEs in the bottled drinks collected in this study posed negligible non-carcinogenic health risks to human health by ingestion [38]. DEHP is the major chemical contributing to the non-carcinogenic risk of PAEs on average, posing non-carcinogenic risk two orders of magnitude higher than that of DBP. Because non-carcinogenic risk is highly associated with the concentrations of PAEs detected in the samples [38], the risk posed by other non-assessed chemicals (e.g., DIBP) is most likely much lower than DEHP.

It has been known that storage time and temperature can significantly impact the migration of chemicals from packaging material to drinks [38]. When bottled drinks are stored at a high temperature for a long time, human health risks posed by the ingestion of chemicals can be increased significantly, especially the carcinogenic risk [38]. Further, co-exposure of a variety of chemical pollutants under long-term chronic exposure may have a considerable total risk to human health. Therefore, the consumption of bottled drinks could be a non-neglectable risk factor contributing to human health risk.

4. Conclusions

In summary, this is the first study to investigate the occurrence and distribution of fifteen PAEs in various types of bottled drinks in China. Our results indicated the widespread occurrence of PAEs in different types of bottled drinks. Drink type is an important factor determining the concentrations of PAEs in the drinks. Significant differences of PAE concentrations between different types of bottled drinks were observed in this study. For example, the median sum concentration of 15 PAEs in soft drink samples is over five times higher than that detected in mineral water samples. Although human exposure doses of PAEs through the consumption of bottled drinks are much lower than the oral reference doses recommended by U.S. EPA, it is non-neglectable, especially considering the high frequency of the consumption of bottled drinks in daily life. Further, the higher carcinogenic risk
posed by DEHP exposure through the consumption of bottled drinks warrants attention from the public.

Our results provide baseline information, for the first time, regarding the occurrence of PAEs in bottled drinks available in the Chinese market, which is helpful for people in choosing appropriate bottled drinks. To minimize PAE exposure, it is recommended to use bottled mineral water, instead of energy drinks, juice drinks, soft drinks, tea drinks, and beer, and avoid the use of bottled drinks with long-term storage at a high temperature. Compared with bottled drinks, tap water is recommended in everyday life. This is especially important for vulnerable members in the community, such as pregnant women, lactating women, infants, and children. Further, it is recommended to develop safer alternatives for DEHP, which is the most frequently observed PAE and can pose a higher carcinogenic risk. Authorities need to take measures to control the content of DEHP present in bottled drinks.

Supplementary Materials: The following are available online, Table S1: title, Detailed information of the 15 PAEs measured in this study; Table S2: title, Instrumental parameters on GC-MS conditions for phthalate analysis; Table S3: title, Concentrations (ng/L) of the target phthalates in procedural blanks and their limits of detection (LOD) and limits of quantification (LOQ); Table S4: title, Correlation coefficients between the new abstract principal components and the PAEs present in the bottled drinks.

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