J Med Sci 2018;38(6):258-268
DOI: 10.4103/jmedsci.jmedsci_52_18

ORIGINAL ARTICLE

Estimated Daily Intake and Cumulative Risk Assessment of Phthalates in Taiwan Military Personnel

Nai-Yueh Ko[1], Yuan-Ting C. Lo[1], Zu-Yi Sia[2], Ya-Chi Lu[1], Jhih-Yuan Wei[2], Ming-Jhou Cai[2], Hsiu-Ying Ku[1], Senyeong Kao[1], Hsien-Liang Su[3], Junn-Liang Chang[4], Han-Bin Huang[1]

[1]National Defense Medical Center, School of Public Health, [2]National Defense Medical Center, Graduate Institute of Life Sciences, Taipei, [3]Physical Examination Center, Taoyuan Armed Forces General Hospital, [4]Department of Pathology and Laboratory Medicine, Taoyuan Armed Forces General Hospital, Taoyuan, Taiwan

Background: Phthalate esters (PAEs), which may have potential adverse health effects, are widely used in industrial and consumer products. The public raised concerns of exposure to PAEs after di-2-ethylhexyl PAE (DEHP) had been illegally used in food products in Taiwan in 2011. However, there is little information regarding the exposure levels of PAEs among Taiwanese military personnel. **Objective:** Health risk assessment indicators, including daily intake (DI), hazard quotient (HQ), and hazard index (HI), were used to assess the distribution and trends of PAEs and cumulative risk in Taiwanese military personnel. **Materials and Methods:** We recruited 503 participants who participated in northern voluntary military service from June to August 2017. We calculated the DI of five PAEs, namely dimethyl PAE, diethyl PAE, dibutyl PAE (DBP), benzyl butyl phthalate, and DEHP, and selected the reference dose (RfD) described by the US Environmental Protection Agency (EPA) as an acceptable exposure reference value to compute the HQ and HI. We used statistical analysis to examine the differences and trends of PAE metabolites in urine and investigated the possible primary sources of PAEs with principal component analysis. **Results:** The detection rates of 7 PAE metabolite concentrations were ≥72.2%. All DIs, HQ_{RfD}s, and HI_{RfD}s were not over the standard EPA RfD. For all participants, two principal components (PC) were extracted. Three DEHP metabolites and MBP were correlated with PC1, and MiBP and MnBP were correlated with PC2. **Conclusions:** The main potential sources of PAE exposure for Taiwanese military personnel are DEHP and DBP. Efforts to reduce exposure to environmental PAEs are necessary to maintain health within the military.

Key words: Military, phthalates, cumulative risk

INTRODUCTION

Phthalate esters (PAEs), which are widely used in consumer products, are readily release polymers from plastic containers under high-temperature conditions. People are frequently exposed to PAEs through ingestion of food and water, dermal exposure, and inhalation of polluted air.[1] Animal studies have reported carcinogenic effects; testicular and ovarian toxicity; and hormonal, hepatic, and renal effects post-PA exposure.[2,3] Adverse health effects on humans depend on individual development stages and exposure duration. Long-term exposure to low doses of PAEs may lead to abdominal obesity, insulin resistance, and other systemic diseases. Such adverse effects may be caused by interference with the endocrine system (e.g., antiandrogens and thyroid hormones) or gene expression.[4-10]

The public raised more concerns of exposure to PAEs after di-2-ethylhexyl PAE (DEHP) had been illegally used in food products in Taiwan in 2011. Subsequently, experts studied PAE exposure among Taiwanese populations,[11-16] health hazards, and food contamination.[17] In addition, previous research indicated that young adults aged 20–40 years are often exposed to high

Received: April 29, 2018; Revised: June 04, 2018; Accepted: July 19, 2018
Corresponding Author: Dr. Han-Bin Huang, National Defense Medical Center, School of Public Health, 161 Minchuan East Road, Sec. 6, Taipei 114, Taiwan. Tel: +886-2-87923100 ext.18441; Fax: +886-2-87923147. E-mail: toly2000@gmail.com

How to cite this article: Ko NY, Lo YTC, Sia ZY, Lu YC, Wei JY, Cai MJ, *et al.* Estimated daily intake and cumulative risk assessment of phthalates in Taiwan military personnel. J Med Sci 2018;38:258-68.

levels of phthalates while compared to the other age groups in adults.[18,19] This age group is the main population in the military and information concerning the levels of phthalates exposure and their distribution in demographic/occupational characteristics among the military personnel is finite. The previous nationwide studies investigated the phthalates exposure in community free-living population and excluded institutionalized persons, which is hard to obtain basic information in military population. The exposures circumstances or health effects related to army is unraveling. We do not have the PAEs exposure levels in army, and it is difficult for us to compare this exposure levels in both populations. To the best of our understanding, there is no study to explore the distribution and cumulative risk of phthalates exposure in Taiwanese military personnel. Thus, the purpose of this study was to determine the distribution of PAE metabolites in urine, daily intakes (DIs) of PAEs, and cumulative risk of exposure (hazard quotient [HQ]; hazard index [HI]) in military personnel.

MATERIALS AND METHODS

Study participants and sampling

We recruited 503 participants who participated in northern voluntary military service and conducted annual physical examinations at the Health Evaluation Center of Taoyuan Armed Forces General Hospital from June to August 2017. In this cross-sectional study, all participants provided a morning spot urine sample. These samples were collected in disposable centrifuge glass tubes with screw caps and rubber liners. Participants completed a structured questionnaire about demographics, medical history, and personal health habits.

The participant recruitment and sampling processes were approved by the Institutional Review Board of the Tri-Service General Hospital, National Defense Medical Center (No. 2-106-05-021). The methods were performed in accordance with the approved guidelines. Informed consent was obtained from all the study participants before the study enrollment.

Measurement of urinary phthalate metabolites

Excluding four pregnant or breastfeeding women, three with thyroid dysfunction, two with diabetes, and 59 with urine creatinine levels outside the normal range of 0.3–3.0 g/L,[20] we measured the concentrations of seven PAEs metabolites, namely monomethyl phthalate (MMP), monoethyl phthalate (MEP), mono-n-butyl phthalate (MBP), monobenzyl phthalate (MBzP), mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) in the spot urine samples collected from 435 participants using solid-phase extraction (SPE) and high-performance liquid chromatography (Agilent Technologies, Santa Clara, CA, USA) tandem mass spectrometry (AB SCIEX, Framingham, MA, USA) (HPLC-MS/MS).[21,22] Creatinine was used to adjust for individual variations in urine concentration.

Procedural blanks were prepared at an interval of every ten samples to confirm whether contamination occurred during sample extraction. Duplicate injection administration and calibration check standards were performed for every ten samples to ensure accuracy and precision. For measurements, the concentrations below the limit of detection (LOD) were replaced by a default value of LOD divided by the square of 2. The value of recovery rate was ranged from 95% to 102% and the coefficients of variation were <5%.

Calculating daily intakes

The distributions of exposure to each PAE in Taiwanese military personnel were measured by calculating the DI for each PAE using the combined urinary PAE metabolite concentrations and individual age, body height, body weight, creatinine concentration, PAE molecular weight data, and other factors.[23] The unit of DI is μg/kg/day, and it is calculated as follows:

$$\mathrm{DI}\left(\mu g / kg_{bw} / day\right) = \frac{UE_{sum}\left(\mu mole / g_{crea}\right) \times CE_{smoothed}\left(g / day\right)}{F_{UE} \times bw\left(kg\right)} \times MW_{Phthalate}\left(g / mole\right)$$

Where UE_{sum} is the molar urinary excretion of the respective metabolite in micromoles per gram creatinine. The smoothed creatinine excretion (CE) rates ($CE_{smoothed}$) are body height-and sex-based reference values for urinary CE according to the study by Mage *et al*.[24] The molar fraction (F_{UE}) describes the molar ratio between the excreted amounts of the specific metabolites of each phthalate corresponding to the dietary intake of the parent phthalate.

The F_{UE} values for MMP, MEP, MBP, MBzP, MEHP, MEHHP, and MEOHP are 0.69, 0.69, 0.69, 0.73, 0.062, 0.0149, and 0.109, respectively.[25-28] $MW_{Phthalate}$ is the molecular weight of parent PAEs and bw is the body weight of each participant.

Cumulative risk assessment: hazard quotient and hazard index

We used the HQ to assess the participant's risk from each phthalate and used the HI to assess the participant's total risk from the PAE in question.[29,30] The formula used was as follows:

$$HQ = \frac{DI}{\text{Reference limit value}}$$

$$HI = \sum_{i=1}^{n} \frac{EL_i}{AL_i}$$

Where EL_i is the exposure level of PAEs, AL_i is the reference limit value (RLV), and n is the number of PAEs with the same health effects. We used the reference dose (RfD) described by the US Environmental Protection Agency (EPA) as the RLV of this study. The RfD values of DEHP, dibutyl PAE (DBP), benzyl butyl phthalate (BBzP), diethyl PAE (DEP), and dimethyl PAE (DMP) are 0.002 mg/kg/day, 0.1 mg/kg/day, 0.2 mg/kg/day, 0.8 mg/kg/day, and 0.2 mg/kg/day, respectively.[31-35] An HI <1 indicates no significant adverse effects from several chemicals exposure could happen.[36]

Principle component analysis

We used principal component analysis (PCA) to identify potential sources of phthalates among seven phthalate metabolites (MMP, MEP, MBP, MBzP, MEHHP, MEOHP, and MEHP). PCA was implemented using a correlation matrix and maximum variation sampling, and factors with an eigenvalue >1 were extracted.

Statistical analysis

IBM SPSS Statistics version 20.0 for Windows (Chicago, Illinois, USA) was used to perform statistical analysis and statistical significance was defined as $P < 0.05$.

To assess the internal exposure to PAEs among military personnel, urinary PAE metabolite concentration and cumulative risk were investigated using the Kruskal–Wallis test, trend test, and Mann–Whitney U-test stratified by age (19–30 years, 31–40 years, and 4–-52 years; men and women were divided separately into each age group), service type (army, navy, and air force), seniority (<5 years, 6–10 years, 11–15 years, and >16 years), and sex (male and female).

RESULTS

Demographic characteristics

The study participants comprised 338 men (77.7%) and 47 women (22.3%), with an average age of 32.16 years. Among the participants, 384 served in the army, 22 in the navy, and 29 in the air force. The average time in service was 10.71 years, which included 120 participants (27.6%) who served for <5 years, 83 (19.1%) who served for 6–10 years, 123 (28.2%) who served for 11–15 years, and 109 (25.1%) who served for >16 years. Regarding health behaviors, 334 (76.8%) had no smoking habit, 421 (96.8%) did not consume betel nut, 231 (53.1%) had no drinking habits, and 419 (96.3%) exercised regularly [Table 1]. In addition, significant differences in the seniority, smoking habit,

Table 1: Demographic characteristics of the study participants

	Analyzed sample	Sex		*P*
	All (*n*=435)	Male (*n*=388)	Female (*n*=47)	
Age group (years)				
19-30	156 (35.9)	134 (34.5)	22 (46.8)	0.099[d]
31-40	246 (56.5)	226 (58.2)	20 (42.6)	
41-52	33 (7.6)	28 (7.2)	5 (10.6)	
Age (years)[a]	32.16±6.43	32.31±6.41	30.87±6.56	0.148[b]
Service				
Army	384 (88.3)	341 (87.9)	43 (91.4)	0.932[d]
Navy	22 (5.1)	20 (5.1)	2 (4.3)	
Air force	29 (6.7)	27 (7.0)	2 (4.3)	
Seniority (year)[a]	10.71±6.45	11.02±6.44	8.14±6.02	
5 years and below	120 (27.6)	102 (26.3)	18 (38.3)	0.004[b]
6-10 years	83 (19.1)	64 (16.5)	19 (40.4)	
11-15 years	123 (28.2)	119 (30.7)	4 (8.5)	
16 years and above	109 (25.1)	103 (26.5)	6 (12.8)	
Smoking habit				
No	334 (76.8)	290 (74.7)	44 (93.6)	0.007[c]
Yes	101 (23.2)	98 (25.3)	3 (6.4)	
Betel nuts				
No	421 (96.8)	374 (96.4)	47 (100.0)	0.381[d]
Yes	14 (3.2)	14 (3.6)	-	
Drinking alcohol				
No	231 (53.1)	197 (50.8)	34 (72.3)	0.008[c]
Yes	204 (46.9)	191 (49.2)	13 (27.7)	
Physical activity				
No	16 (3.7)	11 (2.8)	5 (10.6)	0.007[d]
1-2 days/week	174 (40)	149 (38.4)	25 (53.2)	
3-4 days/week	181 (41.6)	166 (42.8)	15 (31.9)	
5 days/week or more	64 (14.7)	62 (16.0)	2 (4.3)	
Taking Chinese medicine				
No	110 (25.3)	90 (23.2)	20 (42.6)	0.038[c]
Yes	325 (74.7)	298 (76.8)	27 (57.4)	
Drinking water container				
Plastics	271 (62.3)	243 (62.6)	28 (59.6)	0.683[c]
Nonplastics	164 (37.7)	145 (37.4)	19 (40.4)	

[a]Mean±SD, [b]Independent sample *t*-test, [c]Chi-square test, [d]Fisher's exact test. SD: Standard deviation

drinking alcohol, and physical activity between males and females were observed.

Urinary phthalate ester metabolite concentrations

The LOD of MMP, MEP, MBP, MBzP, MEHHP, MEOHP, and MEHP was 0.1 ng/mL, and the detection rates were 72.2%, 99.1%, 99.5%, 100%, 100%, 100%, and 95.2%, respectively.

In the unadjusted model, the median concentrations of the seven PAE metabolites were 0.615, 3.830, 4.240, 0.368, 2.040, 1.100, and 0.759 ng/mL, respectively. In the urinary creatinine-adjusted model, the median concentrations of the seven PAE metabolites were 0.411, 2.643, 2.980, 0.259, 1.582, 0.799, and 0.586 μg/g cr [Table 2]. Strong-to-weak significant positive correlations were found among all PAE metabolites, except MMP (data not shown).

Distribution of daily intake, hazard quotient, and hazard index

The maximum DIs of DMP, DEP, DBP, BBzP, and DEHP were 0.465, 15.46, 4.742, 0.292, and 5.582 μg/kg/day, respectively. All the DIs in this study did not exceed the standard values of EPA RfD (200 μg/kg/day for DMP, 800 μg/kg/day for DEP, 100 μg/kg/day for DBP, 200 μg/kg/day for BBzP, and 20 μg/kg/day for DEHP). Therefore, the HQ_{RfD} of each PAE also did not exceed 1. This indicates that the individual exposure risk of the five PAEs in this study may not have adverse health risk. The maximum HI_{RfD}, which was obtained by summing the HQ_{RfD} values of DMP, DEP, DBP, BBzP, and DEHP, was 0.280, which did not exceed 1. This also indicates that the cumulative exposure risk of the five PAEs in this study may not have adverse health risk [Table 3].

In terms of age and seniority stratification, the median DI and HQ_{RfD} were not significantly different between the groups. Similarly, no significant difference in trend was observed [Table 4]. However, in terms of service hierarchy, the DIs (0.325, 0.319, and 0.226 μg/kg/day, respectively) and HQ_{RfD} (0.325, 0.319, and 0.226, respectively) of DEHP for the army, navy, and air force were significantly different ($P = 0.037$) [Supplementary Table 1].

After sex and age stratification, the median DI and HQ_{RfD} of DMP were significantly different between the female age groups ($P = 0.043$). In addition, the DIs of DBP and BBzP increased with increasing age in women (P for these trends were 0.003 and 0.005). However, no statistical differences were observed in the trends among men. Significant differences were noted in the median DI and HQ_{RfD} of DMP, BBzP, and DEHP in the 31–40 years group by sex (P = F 0.002, 0.0005, and 0.006, respectively), and men generally had higher DI and HQ_{RfD} values than women [Table 5].

Table 2: Urinary phthalate esters metabolite concentrations in the study population (n=435)

Phthalate metabolites	LOD (ng/ml)	n (%) ≥ LOD	Unadjusted (ng/ml)				Creatinine adjusted (μg/g cr.)			
			P_{25}	P_{50}	P_{95}	Maximum	P_{25}	P_{50}	P_{95}	Maximum
MMP	0.1	314 (72.2)	0.071	0.615	6.572	32.70	0.115	0.411	4.414	12.25
MEP	0.1	431 (99.1)	1.760	3.830	27.26	581.0	1.252	2.643	24.34	332.0
MBP	0.1	433 (99.5)	2.470	4.240	16.48	85.80	1.513	2.980	16.21	121.0
MBzP	0.1	435 (100)	0.281	0.368	0.731	17.30	0.178	0.259	0.832	10.71
MEHHP	0.1	435 (100)	1.370	2.040	7.664	156.0	0.908	1.582	6.045	71.53
MEOHP	0.1	435 (100)	0.762	1.100	3.020	13.50	0.486	0.799	2.603	9.14
MEHP	0.1	414 (95.2)	0.393	0.759	3.822	17.60	0.269	0.586	2.789	12.14

LOD: Limit of detection, MMP: Monomethyl phthalate, MEP: Monoethyl phthalate, MBP: Mono-n-butyl phthalate, MBzP: Monobenzyl phthalate, MEHP: Mono (2-ethylhexyl) phthalate, MEOHP: Mono (2-ethyl-5-oxohexyl) phthalate, MEHHP: Mono (2-ethyl-5-hydroxyhexyl) phthalate

Table 3: The distribution of hazard quotient reference dose and hazard index reference dose (n=435)

	Minimum	Percentiles					Maximum	>1 (%)
		P_{25}	P_{33}	P_{50}	P_{67}	P_{95}		
HQ_{RfD}_DMP	3.7×10^{-6}	2.0×10^{-5}	3.9×10^{-5}	7.4×10^{-5}	1.4×10^{-4}	8.1×10^{-4}	2.3×10^{-3}	0 (0)
HQ_{RfD}_DEP	1.4×10^{-6}	6.2×10^{-5}	8.1×10^{-5}	1.3×10^{-4}	2.0×10^{-4}	1.1×10^{-3}	1.9×10^{-2}	0 (0)
HQ_{RfD}_DBP	1.3×10^{-5}	6.3×10^{-4}	8.0×10^{-4}	1.2×10^{-3}	2.0×10^{-3}	6.2×10^{-3}	4.7×10^{-2}	0 (0)
HQ_{RfD}_BBzP	1.4×10^{-5}	3.3×10^{-5}	3.8×10^{-5}	5.0×10^{-5}	6.6×10^{-5}	1.6×10^{-4}	1.5×10^{-3}	0 (0)
HQ_{RfD}_DEHP	2.8×10^{-3}	9.7×10^{-3}	1.1×10^{-2}	1.6×10^{-2}	2.1×10^{-2}	5.0×10^{-2}	2.8×10^{-1}	0 (0)
HI_{RfD}[a]	3.2×10^{-3}	1.1×10^{-2}	1.3×10^{-2}	1.8×10^{-2}	2.5×10^{-2}	5.5×10^{-2}	2.8×10^{-1}	0 (0)

[a]HI_{RfD}=HQ_{RfD}_DMP + HQ_{RfD}_DEP + HQ_{RfD}_DBP + HQ_{RfD}_BBzP + HQ_{RfD}_DEHP. PAE: Phthalates, DMP: Dimethyl PAE, DEP: Diethyl PAE, DBP: Dibutyl PAE, BBzP: Benzyl butyl phthalate, DEHP: Di-2-ethylhexyl PAE, HQ: Hazard quotient, $_{RfD}$: Reference dose

Table 4: The daily intakes and hazard quotient reference dose by (A) age stratified, (B) services stratified, and (C) seniority stratified (n=435)

Phthalate (years)	RfD	Median (minimum-maximum)				
		DMP	DEP	DBP	BBzP	DEHP
A. Age stratified						
19-30 (n=156)	DI	0.015 (0.001-0.370)	0.106 (0.003-15.46)	0.106 (0.002-1.382)	0.009 (0.003-0.195)	0.311 (0.080-5.582)
	HQ	0.00008 (0.000005-0.002)	0.0001 (0.000004-0.019)	0.001 (0.00002-0.019)	0.00004 (0.00001-0.001)	0.015 (0.004-0.279)
31-40 (n=246)	DI	0.014 (0.0007-0.465)	0.103 (0.001-7.155)	0.128 (0.001-4.742)	0.011 (0.003-0.165)	0.323 (0.055-2.437)
	HQ	0.00007 (0.000004-0.002)	0.0001 (0.000001-0.009)	0.001 (0.00001-0.047)	0.0005 (0.00001-0.0008)	0.016 (0.003-0.122)
41-52 (n=33)	DI	0.021 (0.0008-0.091)	0.103 (0.005-1.091)	0.145 (0.042-0.970)	0.008 (0.004-0.292)	0.272 (0.123-0.991)
	HQ	0.0001 (0.000004-0.0005)	0.0001 (0.00001-0.001)	0.001 (0.0004-0.009)	0.00004 (0.00002-0.001)	0.014 (0.006-0.050)
P[a]		0.424	0.919	0.126	0.213	0.457
P for linear trendb		0.640	0.726	0.053	0.830	0.958
B. Services stratified						
Army (n=384)	DI	0.015 (0.0007-0.465)	0.102 (0.001-15.46)	0.123 (0.001-4.742)	0.010 (0.003-0.292)	0.325 (0.055-5.582)
	HQ	0.00007 (0.000004-0.002)	0.0001 (0.000001-0.019)	0.001 (0.00001-0.019)	0.00005 (0.00001-0.001)	0.016 (0.003-0.279)
Navy (n=22)	DI	0.020 (0.001-0.207)	0.097 (0.019-2.231)	0.090 (0.005-1.12)	0.010 (0.005-0.035)	0.319 (0.125-2.114)
	HQ	0.0001 (0.00001-0.001)	0.0001 (0.00002-0.003)	0.0009 (0.00005-0.011)	0.0005 (0.00002-0.0002)	0.016 (0.006-0.106)
Air force (n=29)	DI	0.013 (0.001-0.171)	0.111 (0.004-2.908)	0.113 (0.009-0.266)	0.0009 (0.004-0.023)	0.226 (0.093-2.304)
	HQ	0.00006 (0.00001-0.0009)	0.0001 (0.00001-0.004)	0.001 (0.00009-0.003)	0.00004 (0.00002-0.0001)	0.011 (0.005-0.115)
P[a]		0.995	0.853	0.231	0.466	0.037
C. Seniority stratified						
<5 (n=120)	DI	0.021 (0.001-0.370)	0.085 (0.003-15.459)	0.099 (0.002-1.382)	0.009 (0.003-0.057)	0.301 (0.083-5.582)
	HQ	0.0001 (0.000005-0.002)	0.0001 (0.000004-0.019)	0.001 (0.00002-0.014)	0.00005 (0.00001-0.0003)	0.015 (0.004-0.279)
6-10 (n=83)	DI	0.011 (0.0007-0.175)	0.122 (0.001-7.154)	0.135 (0.003-1.241)	0.010 (0.003-0.195)	0.311 (0.055-5.328)
	HQ	0.00006 (0.000004-0.0009)	0.0001 (0.000001-0.009)	0.001 (0.00003-0.012)	0.00005 (0.00002-0.001)	0.016 (0.003-0.266)
11-15 (n=123)	DI	0.015 (0.001-0.465)	0.093 (0.009-6.513)	0.120 (0.005-0.785)	0.010 (0.004-0.054)	0.310 (0.080-1.525)
	HQ	0.00007 (0.000005-0.002)	0.0001 (0.00001-0.008)	0.001 (0.00005-0.008)	0.00005 (0.00002-0.0002)	0.016 (0.004-0.076)
>16 (n=109)	DI	0.015 (0.0008-0.364)	0.109 (0.005-2.908)	0.155 (0.001-4.742)	0.011 (0.003-0.292)	0.332 (0.083-2.304)
	HQ	0.00008 (0.000004-0.002)	0.0001 (0.00001-0.003)	0.002 (0.00001-0.047)	0.00005 (0.00001-0.001)	0.017 (0.004-0.115)
P[a]		0.332	0.244	0.119	0.476	0.259
P for linear trend[b]		0.800	0.652	0.166	0.494	0.115

[a]Kruskal–Wallis test, [b]All data (such as DIs and HQ) transformed by natural logarithm was applied to perform the trend test. DI: Daily intake, HQ: Hazard quotient, RFD: Reference dose, PAE: Phthalates, DMP: Dimethyl PAE, DEP: Diethyl PAE, DBP: Dibutyl PAE, BBzP: Benzyl butyl phthalate, DEHP: Di-2-ethylhexyl PAE

In terms of age stratification, the major contributor of HQ_{RfD} was DEHP and followed by DBP and DEP [Figure 1]. In terms of service stratification, the major contributor of HQ_{RfD} was DEHP, followed by DBP and DEP. In terms of seniority stratification, the major contributor of HQ_{RfD} was DEHP, followed by DBP and DEP. After sex and age stratification, the major contributor of HQ_{RfD} was DEHP, followed by DBP and DEP. Among the five PAEs contributing to HQ_{RfD}, the major contributor was DEHP, followed by DBP and DEP in all participants stratified by age, service, seniority, and sex.

Principle component analysis

We evaluated the exposure profile of PAEs in all participants stratified by sex and age [Figure 2].

For all participants, two principal components (PCs) were extracted, which accounted for 32.2% (PC1) and 15.4% (PC2) of the variability. This indicated two major potential sources of PAEs among Taiwanese military personnel. The three DHEP metabolites MEHHP, MEOHP, and MEHP and MBP were correlated with PC1, and MEP and MBzP were correlated with PC2.

Table 5: The Daily intakes and Hazard Quotient reference dose by gender and age stratified (*n*=435)

Phthalate	RfD	Median (minimum-maximum)				
		DMP	DEP	DBP	BBzP	DEHP
19–30 years female (*n*=22)	DI	0.012 (0.001–0.177)	0.115 (0.025–2.729)	0.088 (0.031–0.278)	0.008 (0.003–0.023)	0.237 (0.114–5.581)
	HQ	0.00006 (0.000005–0.0009)	0.0001 (0.00003–0.003)	0.0009 (0.0003–0.003)	0.00004 (0.00001–0.0001)	0.119 (0.006–0.279)
31-40 years female (*n*=20)	DI	0.002 (0.0007-0.175)	0.074 (0.013-0.3357)	0.091 (0.003-0.604)	0.007 (0.003-0.026)	0.187 (0.074-1.026)
	HQ	0.00001 (0.000004-0.0009)	0.0009 (0.00002-0.0005)	0.0009 (0.00003-0.006)	0.00003 (0.00001-0.0001)	0.009 (0.004-0.051)
41-52 years female (*n*=5)	DI	0.009 (0.001-0.081)	0.282 (0.019-0.887)	0.121 (0.062-0.812)	0.010 (0.005-0.292)	0.252 (0.236-0.461)
	HQ	0.00004 (0.00001-0.0004)	0.0004 (0.00002-0.001)	0.001 (0.0006-0.008)	0.00005 (0.00003-0.001)	0.013 (0.012-0.023)
P[a]		0.043	0.108	0.294	0.446	0.303
P for linear trend[b]		0.531	0.515	0.079	0.033	0.115
19-30 years male (*n*=134)	DI	0.016 (0.001-0.370)	0.099 (0.003-15.459)	0.110 (0.002-1.382)	0.010 (0.004-0.195)	0.319 (0.080-5.328)
	HQ	0.00008 (0.000005-0.002)	0.0001 (0.000004-0.02)	0.001 (0.00002-0.014)	0.00005 (0.00002-0.001)	0.016 (0.004-0.266)
31-40 years male (*n*=226)	DI	0.015 (0.0008-0.465)	0.104 (0.001-7.154)	0.133 (0.001-4.742)	0.011 (0.004-0.165)	0.338 (0.055-2.437)
	HQ	0.00008 (0.000004-0.002)	0.0001 (0.000001-0.009)	0.001 (0.00001-0.047)	0.00005 (0.00002-0.0008)	0.017 (0.003-0.122)
41-52 years male (*n*=28)	DI	0.025 (0.0008-0.091)	0.086 (0.005-1.091)	0.148 (0.042-0.970)	0.008 (0.004-0.030)	0.284 (0.123-0.991)
	HQ	0.0001 (0.000004-0.0005)	0.0001 (0.00001-0.001)	0.001 (0.0004-0.010)	0.00004 (0.00002-0.0002)	0.014 (0.006-0.050)
P[a]		0.461	0.672	0.331	0.157	0.395
P for linear trend[b]		0.424	0.500	0.1266	0.308	0.928
P value of 19-30 years by gender[c]		0.972	0.454	0.150	0.052	0.137
P value of 31-40 years by gender[c]		0.002	0.201	0.153	0.005	0.006
P value of 41-52 years by gender[c]		0.228	0.120	0.752	0.581	0.841

[a]Kruskal–Wallis test, [b]All data (such as DIs and HQ) transformed by natural logarithm was applied to perform the trend test, [c]Mann–Whitney U-test. DI: Daily intake, HQ: Hazard quotient, RFD: Reference dose, PAE: Phthalates, DMP: Dimethyl PAE, DEP: Diethyl PAE, DBP: Dibutyl PAE, BBzP: Benzyl butyl phthalate, DEHP: Di-2-ethylhexyl PAE

Three PCs were extracted from men, which accounted for 38.4% (PC1), 14.5% (PC2), and 14.3% (PC3) of the variability. The three DEHP metabolites (MEHHP, MEOHP, and MEHP) were correlated with PC1, MEP was correlated with PC2, and MMP was correlated with PC3. Three PCs were extracted from women, which accounted for 31% (PC1), 20.5% (PC2), and 15.1% (PC3) of the variability. MEP and MEHP were correlated with PC1; MBP, MBzP, and MEOHP were correlated with PC2; and MMP and MEHHO were correlated with PC3.

After age stratification, three PCs were extracted from the 19 to 30 age group, which accounted for 32.8% (PC1), 17% (PC2), and 15% (PC3) of the variability. The three DEHP metabolites (MEHHP, MEOHP, and MEHP) were correlated with PC1; MBP and MBzP were correlated with PC2; and MEP was correlated with PC3. Two PCs were extracted from the 31 to 40 age group, which accounted for 40% (PC1) and 15% (PC2) of the variability. The three DEHP metabolites, MBP and MBzP were correlated with PC1 and MEP was correlated with PC2. Two PCs were extracted from the 41 to 52 age group, which accounted for 40.9% (PC1) and 22.5% (PC2) of the variability. MEP, MBP, and MBzP were correlated with PC1; and the three DEHP metabolites (MEHHP, MEOHP, and MEHP) were correlated with PC2.

In service stratification, the results of the army and navy group are similar to all participants, but there is a little different in the air force. We also observed similar patterns in seniority stratification (data not shown).

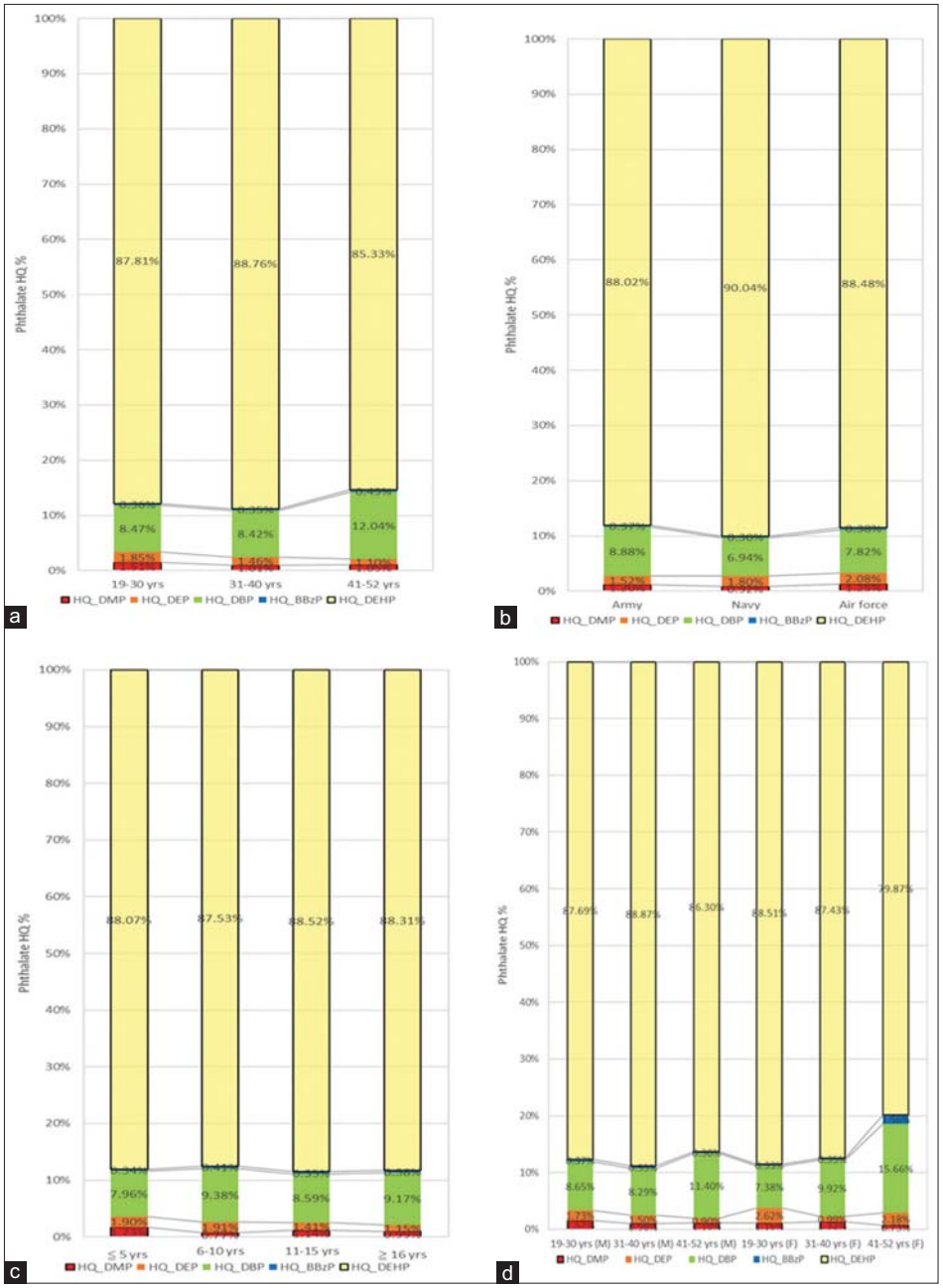

Figure 1: Contribution of different PAEs to hazard quotient. (a) Age stratified, (b) Service stratified, (c) Seniority stratified, (d) Age and Sex stratified

DISCUSSION

Our findings show that participants' PAEs exposure for DIs, HQ_{RfD}s, and HI_{RfD}s were not over the standard EPA RfD. Moreover, two principal components (PC) were extracted. Three DEHP metabolites and MBP were correlated with PC1 and MEP and MBzP were correlated with PC2.

Urinary phthalate ester metabolite concentrations

Using similar age groups, Huang *et al*.[14] studied PAE exposure in the general Taiwanese population in 2013. The MBzP concentration reported in the 18–39-year-old Taiwanese population in their study was similar to that found in this study; however, other values were higher than those in this study. In addition, results obtained in Norwegian (20–66 years old), Belgian (20–39 years old), and

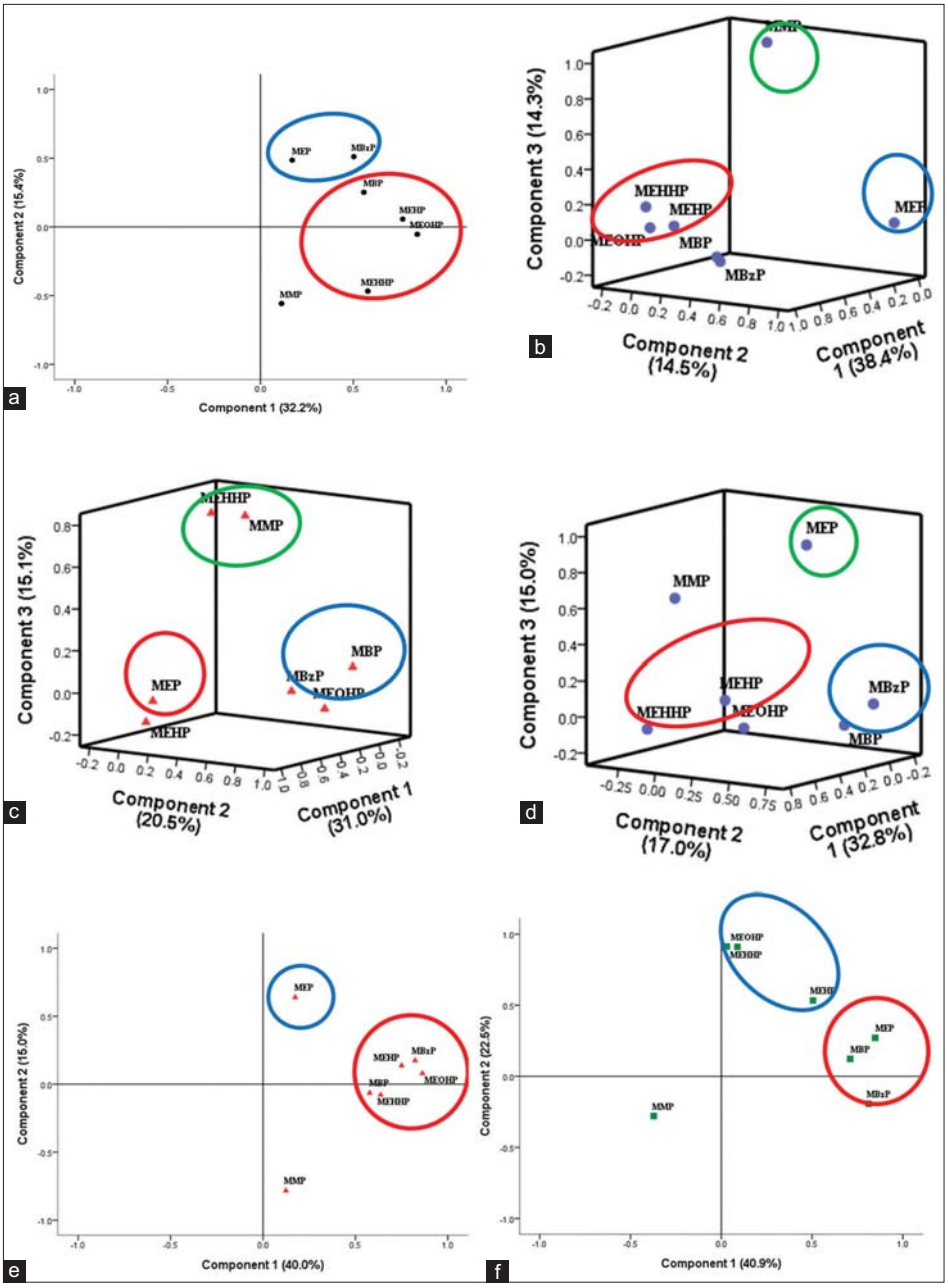

Figure 2: Principal component analysis of seven urinary phthalate metabolites. (a) All participants: 47.6%, (b) male: 67.2%, (c) female: 66.6%, (d) 19–30 years old: 64.8%, (e) 31–40 years old: 55.0%, (f) 41–50 years old: 63.4%

Canadian (20–49 years old) populations were all higher than those obtained in this study [Supplementary Table 2].[37-39] This could be caused by racial and regional differences and may be influenced by different life patterns and exposure status found in the military.

Distribution of daily intake, hazard quotient, and hazard index

Compared with the DIs of the general population with similar age groups (18–39 years old stratified by sex) reported in a study by Chang *et al*.,[19] the DIs in this study were lower, except for BBzP. However, the exposure trends were similar

since the highest DIs were obtained for DEHP in both the studies, followed by DBP and DEP.

The results of a study by Giovanoulis *et al*.[37] in Norway on individuals aged 20–66 years were similar to those of this study in that the DIs obtained in both the studies were lower than the RfD standard. However, the highest DI in the Norwegian study was obtained for DEP, followed by DBP. In addition, Christensen *et al*.[18] studied 18–39-year-olds in the United States, and the DIs of DEHP, DBP, and BBzP were lower than those obtained in this study [Supplementary Table 3].

The HQs and HIs of DMP, DEP, DBP, BBzP, and DEHP were lower than the standard. Compared with the general population with similar age groups in Taiwan in a study by Chang *et al*.,[19] the HI_{RfD} of one man and one woman (18 years or older) exceeded 1 (0.75% and 0.64%, respectively); whereas the study by Christensen *et al*.[18] found that the 95th percentile HI_{TDI} exceeded 1.

Exposure sources of phthalate esters

The results of this study are similar to those of the general population studies in mainland China, Taiwan, and Belgium.[38-41] The main potential source of PAEs is DEHP and other studies indicate that DEHP exposure is closely related to diet.[42,43] For the military personnel in this study, diet may be the most important source of PAEs exposure. The sources of MBP and MBzP include food packaging materials, paints, and lacquers.[44,45] However, the main source of MEP may be personal hygiene products.[46,47] In addition, DMP content is higher in dairy products, instant noodles, cakes, and salted eggs.[42]

Limitations and advantages

The limitations of this study are as follows: (1) the study sample comprised healthy young people who lead a regular life in closed working conditions. As such, the results may not be extrapolated to other ethnic groups; (2) the participants were volunteers who may have better health consciousness, which may have caused selection bias; (3) the PAE metabolite concentrations in this study were obtained from spot urine samples and adjusted with creatinine. The DIs, HQs, and HI were calculated with US RfD. Consequently, these values should be discussed and compared with other research results conservatively; and (4) the studying population was from northern military personnel and did not infer to whole military population. The future studies are needed to explore PAEs levels around other area in the military.

Problems concerning PAE exposure in military personnel have been less investigated. This is the first study to explore the distribution of PAE exposure in Taiwanese military personnel. The study results could elucidate the PAE exposure status in the military and whether these organizations require assistance in reducing PAE exposure.

CONCLUSIONS

The main potential sources of PAE exposure in northern military personnel are DEHP and DBP, which are widely used in food packaging. Therefore, we recommend that measures about how to reduce dietary intake of PAEs (including through washing hands before meals, reducing the use of plastic-packaged foods, and selecting containers that are clearly marked and safe) should be encouraged and added to all health education opportunities.

The respective exposure risks (DI and HQ) of DMP, DEP, DBP, BBzP, and DEHP and cumulative risks (HI) did not exceed the standard EPA RfD. However, the study participants were limited to northern military personnel. Future research should determine the general status of PAE exposure across the entire Taiwanese military by recruiting an equal ratio of participants from seven combat zones. The obtained results could also elucidate whether differences in PAE exposure exist between different regions.

Financial support and sponsorship

The project was financially supported by the Ministry of National Defense (MAB-107-067; MAB-106-097).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Birnbaum LS, Schug TT. Phthalates in our food. Endocr Disruptors 2013;1:e25078.
2. Gray LE Jr., Ostby J, Furr J, Price M, Veeramachaneni DN, Parks L, *et al.* Perinatal exposure to the phthalates DEHP, BBP, and DINP, but not DEP, DMP, or DOTP, alters sexual differentiation of the male rat. Toxicol Sci 2000;58:350-65.
3. Hauser R, Calafat AM. Phthalates and human health. Occup Environ Med 2005;62:806-18.
4. Bajkin I, Bjelica A, Icin T, Dobrić V, Zavisić BK, Stojanoska MM, *et al.* Effects of phthalic acid esters on fetal health. Med Pregl 2014;67:172-5.
5. Diamanti-Kandarakis E, Bourguignon JP, Giudice LC, Hauser R, Prins GS, Soto AM, *et al.* Endocrine-disrupting chemicals: An endocrine society scientific statement. Endocr Rev 2009;30:293-342.
6. Grün F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocr Metab Disord 2007;8:161-71.

7. Kirchner S, Kieu T, Chow C, Casey S, Blumberg B. Prenatal exposure to the environmental obesogen tributyltin predisposes multipotent stem cells to become adipocytes. Mol Endocrinol 2010;24:526-39.
8. Hatch EE, Nelson JW, Qureshi MM, Weinberg J, Moore LL, Singer M, *et al*. Association of urinary phthalate metabolite concentrations with body mass index and waist circumference: A cross-sectional study of NHANES data, 1999–2002. Environ Health 2008;7:27.
9. Shiue I. Higher urinary heavy metal, phthalate, and arsenic but not parabens concentrations in people with high blood pressure, US NHANES, 2011–2012. Int J Environ Res Public Health 2014;11:5989-99.
10. Yaghjyan L, Sites S, Ruan Y, Chang SH. Associations of urinary phthalates with body mass index, waist circumference and serum lipids among females: National Health and Nutrition Examination Survey 1999–2004. Int J Obesity 2015;39:994-1000.
11. Bao J, Zeng XW, Qin XD, Lee YL, Chen X, Jin YH, *et al.* Phthalate metabolites in urine samples from school children in Taipei, Taiwan. Arch Environ Contam Toxicol 2015;69:202-7.
12. Chen CC, Wang SL, Wu MT, Wang YH, Huang PC, Chen BH, *et al.* Exposure estimation for risk assessment of the phthalate incident in Taiwan. PLoS One 2016;11:e0151070.
13. Hsu NY, Lee CC, Wang JY, Li YC, Chang HW, Chen CY, *et al.* Predicted risk of childhood allergy, asthma, and reported symptoms using measured phthalate exposure in dust and urine. Indoor Air 2012;22:186-99.
14. Huang PC, Tsai CH, Liang WY, Li SS, Pan WH, Chiang HC, *et al.* Age and gender differences in urinary levels of eleven phthalate metabolites in general Taiwanese population after a DEHP episode. PLoS One 2015;10:e0133782.
15. Li JH, Ko YC. Plasticizer incident and its health effects in Taiwan. Kaohsiung J Med Sci 2012;28:S17-21.
16. Yen TH, Lin-Tan DT, Lin JL. Food safety involving ingestion of foods and beverages prepared with phthalate-plasticizer-containing clouding agents. J Formos Med Assoc 2011;110:671-84.
17. Wu MT, Wu CF, Wu JR, Chen BH, Chen EK, Chao MC, *et al.* The public health threat of phthalate-tainted foodstuffs in Taiwan: The policies the government implemented and the lessons we learned. Environ Int 2012;44:75-9.
18. Christensen KL, Makris SL, Lorber M. Generation of hazard indices for cumulative exposure to phthalates for use in cumulative risk assessment. Regul Toxicol Pharmacol 2014;69:380-9.
19. Chang JW, Lee CC, Pan WH, Chou WC, Huang HB, Chiang HC, *et al.* Estimated daily intake and cumulative risk assessment of phthalates in the general Taiwanese after the 2011 DEHP food scandal. Sci Rep 2017;7:45009.
20. World Health Oraganization. Biological Monitoring of Chemical Exposure in the Workplace: Guidelines. World Health Oraganization; 1996.
21. Kato K, Silva MJ, Needham LL, Calafat AM. Determination of 16 phthalate metabolites in urine using automated sample preparation and on-line preconcentration/high-performance liquid chromatography/tandem mass spectrometry. Anal Chem 2005;77:2985-91.
22. Janjua NR, Frederiksen H, Skakkebaek NE, Wulf HC, Andersson AM. Urinary excretion of phthalates and paraben after repeated whole-body topical application in humans. Int J Androl 2008;31:118-30.
23. Koch HM, Becker K, Wittassek M, Seiwert M, Angerer J, Kolossa-Gehring M, *et al.* Di-n-butylphthalate and butylbenzylphthalate – Urinary metabolite levels and estimated daily intakes: Pilot study for the German Environmental Survey on children. J Expo Sci Environ Epidemiol 2007;17:378-87.
24. Mage DT, Allen RH, Gondy G, Smith W, Barr DB, Needham LL, *et al.* Estimating pesticide dose from urinary pesticide concentration data by creatinine correction in the third National Health and Nutrition Examination Survey (NHANES-III). J Expo Anal Environ Epidemiol 2004;14:457-65.
25. Anderson WA, Castle L, Scotter MJ, Massey RC, Springall C. A biomarker approach to measuring human dietary exposure to certain phthalate diesters. Food Addit Contam 2001;18:1068-74.
26. Anderson WA, Castle L, Hird S, Jeffery J, Scotter MJ. A twenty-volunteer study using deuterium labelling to determine the kinetics and fractional excretion of primary and secondary urinary metabolites of di-2-ethylhexylphthalate and di-iso-nonylphthalate. Food Chem Toxicol 2011;49:2022-9.
27. Itoh H, Yoshida K, Masunaga S. Quantitative identification of unknown exposure pathways of phthalates based on measuring their metabolites in human urine. Environ Sci Technol 2007;41:4542-7.
28. Koch HM, Angerer JA. Phthalates: Biomarkers and human biomonitoring. Biomarkers Hum Biomonitoring 2011;1:179-233.
29. Kortenkamp A, Faust M. Combined exposures to anti-androgenic chemicals: Steps towards cumulative risk assessment. Int J Androl 2010;33:463-74.
30. Teuschler LK, Hertzberg RC. Current and future risk assessment guidelines, policy, and methods development for chemical mixtures. Toxicology 1995;105:137-44.

31. System UEIRI. Di (2-ethylhexyl) phthalate (DEHP); 1987. Available from: https://www.cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=14. [Last accessed on 2018 Apr 9].
32. System UEIRI. Dibutyl Phthalate; 1987. Available from: https://www.cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=38. [Last accessed on 2018 Apr 9].
33. System UEIRI. Diethyl Phthalate; 1987. Available from: https://www.cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=226. [Last accessed on 2018 Apr 9].
34. System UEIRI. Butyl Benzyl Phthalate; 1989. Available from: https://www.cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=293. [Last accessed on 2018 Apr 9].
35. Kim M, Yun SJ, Chung GS. Determination of phthalates in raw bovine milk by gas chromatography/time-of-flight mass spectrometry (GC/TOF-MS) and dietary intakes. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 2009;26:134-8.
36. Benson R. Hazard to the developing male reproductive system from cumulative exposure to phthalate esters – Dibutyl phthalate, diisobutyl phthalate, butylbenzyl phthalate, diethylhexyl phthalate, dipentyl phthalate, and diisononyl phthalate. Regulatory Toxicol Pharmacol 2009;53:90-101.
37. Giovanoulis G, Alves A, Papadopoulou E, Cousins AP, Schütze A, Koch HM, *et al.* Evaluation of exposure to phthalate esters and DINCH in urine and nails from a Norwegian study population. Environ Res 2016;151:80-90.
38. Dewalque L, Pirard C, Charlier C. Measurement of urinary biomarkers of Parabens, benzophenone-3, and phthalates in a Belgian population. Biomed Res Int 2014;2014:649314.
39. Saravanabhavan G, Guay M, Langlois É, Giroux S, Murray J, Haines D. Biomonitoring of phthalate metabolites in the Canadian population through the Canadian Health Measures Survey (2007–2009). Int J Hyg Environ Health 2013;216:652-61.
40. Gao CJ, Liu LY, Ma WL, Ren NQ, Guo Y, Zhu NZ, *et al.* Phthalate metabolites in urine of Chinese young adults: Concentration, profile, exposure and cumulative risk assessment. Sci Total Environ 2016;543:19-27.
41. Dewalque L, Charlier C, Pirard C. Estimated daily intake and cumulative risk assessment of phthalate diesters in a Belgian general population. Toxicol Lett 2014;231:161-8.
42. Guo Y, Zhang Z, Liu L, Li Y, Ren N, Kannan K, *et al.* Occurrence and profiles of phthalates in foodstuffs from China and their implications for human exposure. J Agric Food Chem 2012;60:6913-9.
43. Koch HM, Lorber M, Christensen KL, Pälmke C, Koslitz S, Brüning T. Identifying sources of phthalate exposure with human biomonitoring: Results of a 48 h fasting study with urine collection and personal activity patterns. Int J Hyg Environ Health 2013;216:672-81.
44. Calafat AM, McKee RH. Integrating biomonitoring exposure data into the risk assessment process: Phthalates [diethyl phthalate and di (2-ethylhexyl) phthalate] as a case study. Environ Health Perspect 2006;114:1783-9.
45. Cao XL. Phthalate esters in foods: Sources, occurrence, and analytical methods. Comprehensive Rev Food Sci Food Safety 2010;9:21-43.
46. Bao J, Wang M, Ning X, Zhou Y, He Y, Yang J, *et al.* Phthalate concentrations in personal care products and the cumulative exposure to female adults and infants in Shanghai. J Toxicol Environ Health A 2015;78:325-41.
47. Guo Y, Wang L, Kannan K. Phthalates and parabens in personal care products from China: Concentrations and human exposure. Arch Environ Contam Toxicol 2014;66:113-9.

Supplementary Table 1: The phthalate metabolite concentrations (ppb; µg/L) by (A) age stratified, (B) services stratified, and (C) seniority stratified (*n*=435)

Phthalate	Median (minimum-maximum)						
	MMP	MEP	MBP	MBzP	MEHHP	MEOHP	MEHP
A. Age stratified							
19-30 years (*n*=156)	0.717 (0.071-20.20)	4.360 (0.071-581.0)	4.040 (0.138-30.70)	0.342 (0.245-8.810)	1.920 (0.203-156.0)	1.110 (0.400-13.50)	0.771 (0.071-17.60)
31-40 years (*n*=246)	0.579 (0.071-32.70)	3.515 (0.071-340.0)	4.245 (0.071-85.80)	0.381 (0.242-2.110)	2.095 (0.374-33.500)	1.070 (0.250-7.150)	0.764 (0.071-12.10)
41-52 years (*n*=33)	1.040 (0.071-5.850)	3.710 (0.222-52.80)	5.510 (0.884-51.30)	0.337 (0.254-17.30)	2.240 (0.927-6.760)	1.160 (0.404-4.210)	0.668 (0.071-5.380)
P[a]	0.165	0.406	0.039	0.150	0.096	0.179	0.829
P for linear trend[b]	0.466	0.987	0.009	0.205	0.200	0.162	0.560
B. Services stratified							
Army (*n*=384)	0.628 (0.071-32.70)	3.780 (0.071-581.0)	4.140 (0.071-85.80)	0.373 (0.242-17.30)	2.040 (0.190-156.0)	1.100 (0.236-13.50)	0.744 (0.071-17.60)
Navy (*n*=22)	0.808 (0.071-6.170)	3.910 (0.521-73.60)	4.870 (0.129-15.30)	0.416 (0.252-0.932)	3.110 (0.797-13.20)	1.380 (0.393-5.340)	1.365 (0.133-121.0)
Air force (*n*=29)	0.498 (0.071-121.0)	7.400 (0.071-51.30)	3.500 (0.560-22.50)	0.350 (0.242-1.240)	1.710 (0.203-49.70)	0.988 (0.256-5.410)	0.609 (0.214-2.340)
P[a]	0.871	0.350	0.361	0.210	0.195	0.583	0.030
C. Seniority stratified							
<5 years (*n*=120)	0.734 (0.071-22.20)	4.330 (0.070-581.0)	3.745 (0.138-37.20)	0.331 (0.245-2.350)	2.035 (0.203-156.0)	1.115 (0.400-7.820)	0.745 (0.071-9.070)
6-10 years (*n*=83)	0.571 (0.071-9.750)	4.495 (0.071-340.0)	4.320 (0.154-26.80)	0.396 (0.249-8.810)	1.850 (0.391-45.40)	1.110 (0.281-13.50)	0.775 (0.071-17.60)
11-15 years (*n*=123)	0.660 (0.071-32.70)	3.270 (0.137-197.0)	3.850 (0.129-41.30)	0.374 (0.242-0.967)	1.965 (0.190-16.70)	0.994 (0.236-5.340)	0.768 (0.071-8.910)
>16 years (*n*=109)	0.546 (0.071-18.60)	3.660 (0.222-52.80)	4.830 (0.071-85.80)	0.381 (0.249-17.30)	2.490 (0.374-33.50)	1.170 (0.250-7.150)	0.767 (0.071-6.680)
P[a]	0.262	0.295	0.100	0.061	0.007	0.078	0.913
P for linear trend[b]	0.056	0.472	0.759	0.625	0.241	0.920	0.169

[a]Kruskal–Wallis test, [b]All data (such as DIs and HQ) transformed by natural logarithm was applied to perform the trend test. MMP: Monomethyl phthalate, MEP: Monoethyl phthalate, MBP: Mono-n-butyl phthalate, MBzP: Monobenzyl phthalate, MEHP: Mono (2-ethylhexyl) phthalate, MEOHP: Mono (2-ethyl-5-oxohexyl) phthalate, MEHHP: Mono (2-ethyl-5-hydroxyhexyl) phthalate, DI: Daily intake, HQ: Hazard quotient

Supplementary Table 2: Estimated phthalate metabolite concentrations from selected studies populations

Author (year)	country	Study subjects	Median of phthalate metabolite concentrations (μg/g cr.)						
			MMP	MEP	MBP	MBzP	MEHHP	MEOHP	MEHP
This study (2018)	Taiwan	Military Age: 19-52 years *n*=435	0.411	2.643	2.98	0.259	1.582	0.99	0.586
Giovanoulis *et al*.(2016)	Norway	Adult Age: 20-66 years *n*=61	<LOQ	17.5-33.1	9.1-11.4	3.0-4.4	4.7-5	4.5-4.9	<LOQ
Huang *et al*.(2015)	Taiwan	Young adult Age: 18-39 years *n*=73	23.9	19.7	16.6	ND	17.7	11.0	6.8
Dewalque *et al*.(2014)	Belgium	General population Age: 20-39 years *n*=99	-	27.5	24.8	4.2	7.3	4.6	2.8
Saravanabhavan *et al*.(2013)	Canada	Young Adult Age: 20-49 years *n*=1205	-	58.8	20.8	10.5	20.7	12.6	4.1

<LOQ: Below the Limit of quantitation, ND: Not detected, MMP: Monomethyl phthalate, MEP: Monoethyl phthalate, MBP: Mono-n-butyl phthalate, MBzP: Monobenzyl phthalate, MEHP: Mono (2-ethylhexyl) phthalate, MEOHP: Mono (2-ethyl-5-oxohexyl) phthalate, MEHHP: Mono (2-ethyl-5-hydroxyhexyl) phthalate

Supplementary Table 3: Estimated daily intakes from selected studies populations

Author (year)	country	Population	Median of daily Intakes (μg/kg/day)				
			DMP	DEP	DBP	BBzP	DEHP
This study (2018)	Taiwan	Military Age: 19-52 years *n*=435	0.015	0.104	0.12	0.006	0.313
Chang *et al*.(2017)	Taiwan	Young Adult Age: 18-39 years *n*=68 (31 male, 37 female)	-	0.856 (male) 0.581 (female)	0.581 (male) 0.624 (female)	0.006 (male) 0.006 (female)	4.03 (male) 2.31 (female)
Giovanoulis *et al*.(2016)	Norway	Adult Age: 20-66 years *n*=61	0.010	0.89	0.39	0.13	0.76
Christensen *et al*.(2014)	U.S.	Young Adult Age: 18-39 years *n*=1430 (676 male, 754 female)	-	-	0.5 (male) 0.6 (female)	0.3 (male) 0.3 (female)	3.9 (male) 4.29 (female)

PAE: Phthalates, DMP: Dimethyl PAE, DEP: Diethyl PAE, DBP: Dibutyl PAE, BBzP: Benzyl butyl phthalate, DEHP: Di-2-ethylhexyl PAE