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Receptor-based aggregate exposure assessment of phthalates based on individual's simultaneous use of multiple cosmetic products

Miyoung Lim[a], Ji Young Park[b], Jae-Eun Lim[c], Hyo-Bang Moon[c], Kiyoung Lee[a,b,*]

[a] Department of Environmental Health Sciences, Graduate School of Public Health, Seoul National University, Seoul, South Korea
[b] Institute of Health and Environment, Seoul National University, Seoul, South Korea
[c] Department of Marine Science and Convergence Engineering, Hanyang University, Ansan, South Korea

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ABSTRACT

To estimate realistic exposure to a chemical, the aggregate exposure from multiple consumer products should be considered. A receptor-based aggregate exposure assessment was conducted according to individuals' exposure factors and simultaneous use patterns including co-use and non-use. A product-based aggregate exposure assessment was conducted by product usage rates of population and users' exposure factors. Two aggregate exposure assessments were compared. Exposure factors for 31 cosmetic products were collected by face-to-face interviews with 1001 members of the Korean population through national representative sampling. The concentrations of phthalates in 214 cosmetic products were analyzed by GC-MS-MS. The average aggregate exposure dose (AED) determined by the receptor-based method for di(2-ethylhexyl)phthalate (DEHP), di-n-butyl phthalate (DnBP), and diethyl phthalate (DEP) were 0.68 ± 0.87, 1.08 ± 5.71, and 2.47 ± 9.05 μg/kg/day, respectively. The cosmetics that contributed most to the receptor-based AED were skin care and body care products for DEHP, nail care products for DnBP, and fragrance and hair care products for DEP. The young female group showed the highest exposure. The product-based aggregate exposure assessment method underestimated high exposure but overestimated average exposure for DnBP and DEP. The receptor-based aggregate exposure assessment method would be used to determine high exposure groups.

1. Introduction

Individuals are exposed to chemical pollutants during their daily lives through multiple sources and routes. Consumer products such as cosmetics, personal care products, and home care products can make our lives more convenient; however, they are the main sources of chemical exposure (Ginsberg and Balk, 2016; Glegg and Richards, 2007). The use of consumer products has been associated with adverse health effects, such as the effect of fragrance products on asthma (Steinemann, 2018), allergic contact dermatitis (Cheng and Zug, 2014) and mucosal symptoms (Elberling et al., 2005). To respond to and manage the potential risk of chemical exposure, the importance of an accurate exposure assessment is growing.

For a realistic exposure assessment of chemicals, combined assessment of multiple sources and routes is needed. This differs from traditional exposure assessments, which are often limited to a single compound with a single exposure pathway. Aggregate exposure is the combined exposure to a single chemical across multiple routes and sources, and cumulative exposure is the combined exposure of a single biological target to multiple chemicals via multiple routes (US EPA, 2003). As concerns about combined exposures to chemicals have increased, the framework for aggregate/cumulative risk assessments of chemical mixtures have been proposed by various organizations (Meek et al., 2011; Pose-Juan et al., 2016).

With regard to the multiple sources and pathways of chemical exposure, aggregate exposure assessment tools for cosmetics and personal care products have recently been developed in Europe (Dudzina et al., 2015; McNamara et al., 2007). Aggregate exposure assessment can be divided into two approaches: product based and receptor based. The product-based approach, also called the population exposure method, estimates the aggregate exposure dose (AED) as a product exposure dose by considering the use rates of the population and the exposure dose of product users (Hall et al., 2007). Some case studies on fragrance ingredients (Safford et al., 2015, 2017) have integrated databases to expand the target population for aggregate exposure estimation (Comiskey et al., 2015, 2017). The receptor-based approach is similar

* Corresponding author. Department of Environmental Health Sciences, Graduate School of Public Health, Seoul National University, 1 Gwanak-ro, Gwanak-gu, Seoul, 08826, South Korea.
E-mail address: cleanair@snu.ac.kr (K. Lee).

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to individual exposure scenarios (Delmaar and van Engelen, 2006), and case studies have been conducted on parabens (Gosens et al., 2014), UV filter substance (Manova et al., 2015), and cyclic siloxane substance (Dudzina et al., 2015) in consumer products.

The receptor-based aggregate exposure of a chemical should include only the products that the individual actually uses. The individual's simultaneous use patterns, exposure factors to each product, and the target chemical concentration of each product are needed for receptor-based aggregate exposure assessment. Previous receptor-based studies have used a model population through repeated sampling from a small survey population, which cannot represent the entire national population (Gosens et al., 2014). When exposure factors are obtained from a representative population sample of sufficient size, the aggregate exposure distribution of the total population can be determined. Furthermore, many aggregate exposure studies have conduct assessments using chemical concentrations reported in the literature (Delmaar et al., 2015; Dudzina et al., 2015) or other limited sources (Safford et al., 2015, 2017). The actual concentrations of target chemicals in the target products must be known for an accurate aggregate exposure assessment.

Among the chemicals mainly used in consumer products, plasticizers, preservatives, waterproofing agents, and flame retardants are known to be endocrine-disrupting chemicals (EDCs) and there is increasing concern about their adverse human health effects. Phthalates are well-known EDCs that are widely used in consumer products as additives and as plasticizers in plastics. Numerous studies have examined the health effects of phthalate exposure on the human body, including male reproductive effects; breast cancer; weight gain and obesity; development of allergies and asthma; and epigenetic modulation (Benjamin et al., 2017; Lottrup et al., 2006; Radke et al., 2018; WHO/UNEP et al., 2013; Zuccarello et al., 2018). The major exposure route of low-molecular-weight phthalates, for example di-n-butyl phthalate (DnBP) and diethyl phthalate (DEP), is non-dietary sources such as cosmetics and personal care products (Giovanoulis et al., 2018; Koch et al., 2013).

The aims of this study were to estimate the AED of phthalates through a receptor-based aggregate exposure assessment for cosmetic products and to compare the results with those of a product-based aggregate exposure assessment. Three phthalates, namely di(2-ethylhexyl)phthalate (DEHP), DnBP, and DEP, were selected as target chemicals. The receptor-based aggregate exposure was estimated from individuals' exposure factors considering multiple cosmetics and actual phthalate concentrations. In addition, the contribution of each product category to the receptor-based AED (AED_r) was determined.

2. Materials & methods

2.1. Collection of exposure factors

A total of 1001 subjects over 19 years old from 17 metropolitan areas and provinces in Korea participated in the exposure factor survey from June to August 2017. The number of subjects was determined by proportionate quota sampling based on the total population composition ratio considering sex, age, and regional distribution. Field survey staff visited homes and collected product use information through face-to-face interviews using a structured questionnaire. The home-visit survey was approved by the Institutional Review Board of the Seoul National University (SNU IRB No. 1608/001-020).

The exposure factors of 31 cosmetic products from nine categories (4 skin care, 3 hair care, 4 body care, 3 cleansing, 4 base makeup, 4 eye makeup, 5 lip makeup, 3 nail care, and 3 fragrance products) were collected. The questionnaire was designed to investigate the use pattern of cosmetic products. Cosmetic products were divided into 69 subtypes by considering the various product types, such as liquid, trigger spray, cream and solid, that exist in the market for each product. The questionnaire was structured to assess the use of each subtype within the past year, and only users of the subtype replied to questions regarding the use frequency, use amount, and brand name of products used. Where several products could be used at the same time for cosmetic purposes, such as face creams, the questionnaire was designed to assess each product individually.

To estimate the single use amount of the product, different types of questions for each subtype were presented. For the most representative liquid, lotion, cream, and foam-type products, five cards showing different product sizes (Park et al., 2015) was provided. Survey participants answered the most similar size of example card for cream-type products, the number of pumps for trigger-type products, the duration of spraying or rubbing for spray- and solid-type products, and the number of tissues used at one time for tissue-type products. In the laboratory, the mass of each unit was measured according to the response patterns. For some colored cosmetic products, such as mascara and lipstick, it was difficult to quantitatively measure the amount used. In these cases, the value published by the Korea Ministry of Food and Drug Safety was used, i.e., the difference between the product's mass before and that after use for 2 weeks (MFDS, 2016).

2.2. Chemical analysis

A total of 214 products were purchased from a market, with at least 3 products in each of the 69 product subtypes. Products were selected in two stages. First, cosmetic brands were selected based on survey results for each product subtype. Second, specific products were selected based on the sales ranking of a Korean online shopping intermediary site. The DEHP, DnBP, and DEP concentrations in 214 products representing 31 cosmetic types was measured.

2.2.1. Sample preparation

Three phthalates (DEP, DnBP, and DEHP) were purchased from AccuStandard (New Haven, CT, USA), and their corresponding deuterated (d4) internal standards were prepared following a method described elsewhere, with minor modifications (Guo and Kannan, 2013; Guo et al., 2014). After spiking 500 ng of d4-DEP, d4-DnBP, and d4-DEHP to cosmetic samples (~0.03 g), 2 mL of Mili-Q water was added, and the mixtures were equilibrated overnight at room temperature. Samples were then extracted twice with 4-mL aliquots of methyl tert-butyl ether (MTBE) by shaking on a horizontal shaker for 30 min and then centrifuged at 4500 g for 10 min. The supernatants were combined, transferred to 15-mL polypropylene tubes, and concentrated to near dryness under a gentle nitrogen stream. The extract was reconstituted with 1 mL of hexane, vortex mixed, and placed in a vial for instrumental analysis.

2.2.2. Instrumental analysis

For the identification and quantification of phthalates, gas chromatography (Agilent Technologies 7890B) coupled to a tandem mass spectrometer (Agilent Technologies 7000C) was used. A fused-silica capillary column (DB-5; 30 m length, 0.25 mm internal diameter, 0.25 μm film thickness) was used for the separation of phthalates. The oven temperature was programmed from 50 °C (held for 3.0 min) to 230 °C at 10 °C/min and 230 °C–300 °C at 5 °C/min. The multiple reaction monitoring (MRM) mode was used; MRM transitions are presented in Table S1. The instrumental limits of quantification (iLOQ) for DEP, DnBP, and DEHP were 5.2, 6.4, and 41.6 ng/g, respectively. The iLOQ was calculated as 10 times the standard deviation of the lowest calibration point. The sample was diluted and reanalyzed when concentrations exceeded the instrument's calibration range.

2.2.3. Quality assurance/quality control

For each bath of samples analyzed, two procedural blanks and solvent (hexane) were injected to check the procedural contamination and carryover between samples. Relatively low concentrations of phthalates, i.e., 3.6, 4.5, and 116 ng/g for DEP, DnBP, and DEHP, respectively, were detected in blank samples. The concentrations detected in procedural blanks were subtracted from the concentrations in samples. The mean recoveries of deuterated phthalates used as internal standards ranged from 86 to 110%. Known amounts of native and internal standards (ng/mL) were injected for every two batches to check instrumental stability; results showed that the relative standard variation (RSD) ranged from 3.07 to 13.6%.

2.3. Receptor-based aggregate exposure assessment

The AED_r (μg/kg/day) values for 1001 participants were calculated form the information on each individual's cosmetic use. Individual AED values were calculated using following equation:

$$AED(\mu g/kg/day) = \sum_{i=1}^{n} \frac{C_i(\mu g/g) \times f_i(use/day) \times q_i(g/use) \times RF_i}{BW\ (kg)}$$

where n is the number of products used by an individual, C_i is the phthalate concentration in these cosmetic products (μg/g), f_i is the frequency of cosmetic use (use/day), q_i is the amount of cosmetic use (g/use), RF_i is the retention factor on the skin (unitless), and BW is the body weight (kg).

The types and numbers of cosmetic products used by individuals and the use frequency (f_i) and use amount (q_i) of each product were obtained from the survey results. The values of C_i used for DEHP, DnBP, and DEP were the maximum value for each cosmetic product. The value of RF was 1 for leave-on cosmetic products and 0.01 for wash-off cosmetic products (SCCS, 2015). Only cleansing products such as hand washes, face cleansers, and shaving foam were classified as wash-off products. The BW value used in the calculation was taken from the participant's actual questionnaire answer.

2.4. Comparison of product-based AED (AED_p) and receptor-based AED (AED_r)

The receptor-based and product based AEDs were compared (Fig. 1). The AED_p of cosmetic products was calculated as the sum of each product's exposure dose by product users considering the population product use rate. Each percentile value of the AED_p was estimated as the sum of each percentile value multiplied by the use rate for 31 cosmetic products. Because the sample size was sufficiently large (1,001), the distribution of AEDs was estimated by the deterministic method in percentile units.

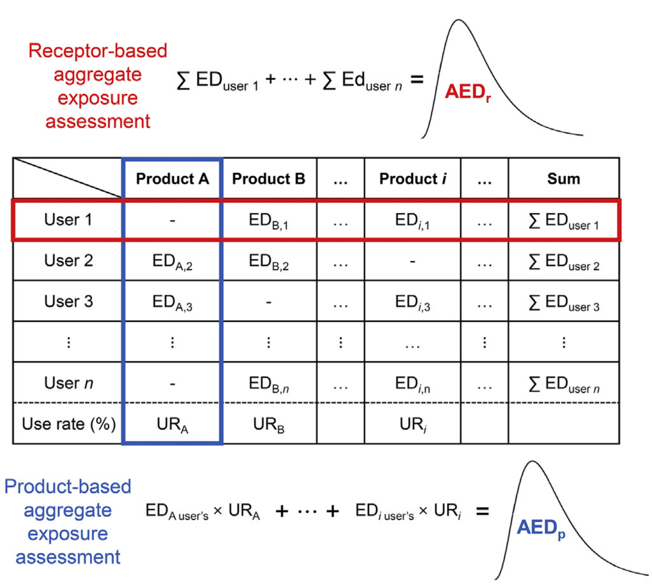

Fig. 1. The concepts of receptor-based and product-based aggregate exposure assessment. $ED_{i,1}$ is exposure dose of product i for user 1. $ED_{A\ user's}$ is exposure dose of product A users and UR_A is use rate of product A in entire population.

2.5. Data analysis

Chi-square tests were used to analyze the use rates by gender and age group. One-way ANOVA was used to analyze use frequency, use amount, and daily mass of product per use by product type and population group. Two-way ANOVA was used to analyze the AED of the three phthalates by gender and age group. All calculations and statistical analyses were conducted using SPSS ver. 23 (IBM Corp., Armonk, NY, USA).

The contributions of the nine cosmetic product categories to the AED were calculated by population group. The population was divided into 10 groups, i.e., two gender groups (female and male) by five age groups (19–29, 30–39, 40–49, 50–59, and ≥60 years). The product contributions were estimated from the ratio of the sum of individual AEDs in the population group to the sum of exposure doses in each product category.

3. Results

3.1. Demographic characteristics of the study population

The demographic characteristics of the 1001 study population are summarized in Table 1. The participants were 50.8% male and 49.2% female. The participants were divided into five age groups: 19–29, 30–39, 40–49, 50–59, and ≥60 years; they were evenly distributed. The most common household income level was between 2000 and 4000 US dollars per month, and the most common education group comprised those with college education or beyond. The proportions of individuals in each household income, education, and marital category were significantly different by gender ($p < 0.01$). The average participant body weight was 56.9 ± 6.5 kg in females and 71.4 ± 9.5 kg in males.

Table 1
Demographic characteristics of the study population (n, %).

	Female		Male		Pooled	
Total number	492	49.2	509	50.8	1001	
Age (years)						
19–29	93	18.9	102	20.0	195	19.5
30–39	98	19.9	103	20.2	201	20.1
40–49	115	23.4	118	23.2	233	23.3
50–59	112	22.8	114	22.4	226	22.6
60+	74	15.0	72	14.1	146	14.6
Household monthly income						
< $2000	32	6.5	30	5.9	62	6.2
$2000–4000	154	31.3	212	41.7	366	36.8
$4000–6000	228	46.3	187	36.7	415	41.8
> $6000	77	15.7	74	14.5	151	15.2
Education						
< Middle school	28	5.7	22	4.3	50	5.0
High school	247	50.2	212	41.7	459	45.9
> College	210	42.7	259	50.9	491	49.1
Marital status						
Single	111	22.6	171	33.6	282	28.2
Married	369	75.0	325	63.9	694	69.3
Divorced/Separated	12	2.4	13	2.6	25	2.5
Body weight (kg, mean ± SD)	56.86 ± 6.45		71.39 ± 9.48		64.25 ± 10.91	

Table 2
Classification of cosmetic products and the number of respondents who used the products (n = 1001).

Category (number of respondents)	Cosmetic products (number of respondents)	Sub product types (number of respondents)
Skincare (959)	Skin toner (907)	Liquid type (491), second liquid type product (31), third liquid type product (1), gel type (41), aerosol spray type (23), pump spray type (36), skin toner for men (399)[a], aftershave (2)
	Face lotion (903)	Lotion type (501), second lotion type product (123), third lotion type product (5), lotion for men (405)[a]
	Face cream (473)	Cream type (457), second cream type product (43), third cream type product (4), eye cream (161)
	Facial sunscreen (596)	Lotion type (391), cream type (191), balm/solid type (9)
Hair care (564)	Hair dye (171)	Bubble type (32), cream type (135), powder type (7)
	Hair treatment (362)	Lotion type (339), pump spray type (25)
	Hair styling (195)	Gel type (78), wax type (80), aerosol spray type (43)
Body care (680)	Body lotion (538)	Lotion type (493), oil type (47)
	Hand cream (490)	–
	Deodorant (69)	Roll-on type (21), stick type (27), aerosol spray type (24)
	Body sunscreen (121)	Cream type (78), roll-on/stick type (22), aerosol spray type (20), pump spray type (1)
Cleanser (903)	Hand wash (180)	Bubble type (124), gel type (28), soap type (31)
	Face cleanser (867)	Foam type (556), bubble type (44), oil type (101), water type (33), cream type (50), lip-and-eye remover type (25), tissue type (50), soap type (39), powder type (3)
	Shaving cream (97)	–
Base makeup (459)	Foundation (415)	BB/CC cream (197), liquid foundation type (125), cushion foundation type (244)
	Makeup base/primer (46)	–
	Pact/powder (167)	–
Eye makeup (344)	Eyeliner (146)	–
	Eyeshadow (236)	–
	Mascara (162)	–
	Eyebrow (215)	–
Lip makeup (488)	Lip balm (82)	–
	Lip Tint (74)	–
	Lip gloss (88)	–
	Lipstick (415)	Stick type (414), pencil type (12)
Nail care (102)	Nail polish (105)	
	Gel nail polish (37)	–
	Nail strengthener (27)	–
	Nail remover (112)	–
Fragrance (313)	Shower cologne (66)	Body mist type (34), cologne type (37)
	Perfume (277)	Perfume for women (224), Perfume for men (55)

[a] Men's products were classified separate subtypes.

3.2. Exposure factors

3.2.1. Use rates of cosmetic products

The classification of the cosmetic products (9 categories; 31 products; 69 subtypes) and the number of respondents who used each cosmetic product at least once in the last year are summarized in Table 2. The categories were classified according to body part (face, hair, body, eye, lip, and nail) and purpose (care, cleansing, and makeup). Skin care products had the greatest number of users (959 of 1001) among the nine categories. The cleanser, body care, and hair care categories were used by more than 50% of respondents.

The use rates of the 31 cosmetic products ranged from 2.7 to 90.6%. Skin toner had the highest use rate (90.6%), followed by face lotion (90.2%), face cleanser (86.6%), facial sunscreen (59.5%), and body lotion (53.7%), whereas nail strengthener and gel nail polish had the lowest use rates, 2.7 and 3.7% respectively. For the skincare products, 31 of 491 users of skin toner, 123 of 501 users of face lotion, and 43 of 457 users of face cream used more than one product from the same subtype. Face cleanser had the greatest diversity of sub-products (foam, bubble, oil, water, cream, lip- and eye-makeup remover, tissue, soap, and powder).

The use rates of cosmetic products differed by gender and age groups (see Table S2). Makeup products, such as base, eye, and lip makeup and nail care categories were mainly used by females. In the case of lip makeup products, the product preference changed by age group, with the young group using lip tint more frequently and the senior group using lipstick more frequently. The use rates differed significantly among the 10 population groups by both gender and age ($p < 0.001$) for all 31 cosmetic products.

3.2.2. Daily mass of cosmetic products

The daily mass (g/day) was calculated for the 31 cosmetic products by multiplying the use frequency (use/day) by the use amount (g/use). The statistical values of the exposure factors for the 69 product subtypes are presented in Table S3. Shaving cream and face cleanser were the products with the highest average daily mass. Skin care products, such as skin toner, face lotion, and face cream, were usually applied twice a day, and the daily mass used was high. Although lip makeup products were used more than twice a day, the daily mass was low because the amount applied was very small. Large variation was observed in the daily mass of body care products that were used over a wide area of the body. There was no gender difference ($p > 0.05$) in the daily mass of skin care, hair care, and body care products applied among product users.

3.3. Phthalate concentrations in cosmetic products

The detection frequency and concentrations of three phthalates in 31 cosmetic products are shown in Table S4. DEHP was the most frequently detected (66.8%) phthalate in the 214 samples analyzed, followed by DnBP (45.3%), and DEP (19.2%). Among the nine categories of cosmetic products, DEHP was found frequently in lip makeup products (16 of 16) and fragrance products (12 of 13). In the other five categories, except base makeup products, the detection frequency was more than 50%. Di-n-butyl phthalate was detected most frequently in nail care products (27 of 31) and had a detection frequency of more than 50% in eye makeup, base makeup, and cleansing products. Diethyl phthalate was mainly detected in hair care products (15 of 15) and fragrance products (11 of 13).

The maximum DEHP concentration (75.24 μg/g) was detected in face cleanser within the cleansing products category. The maximum

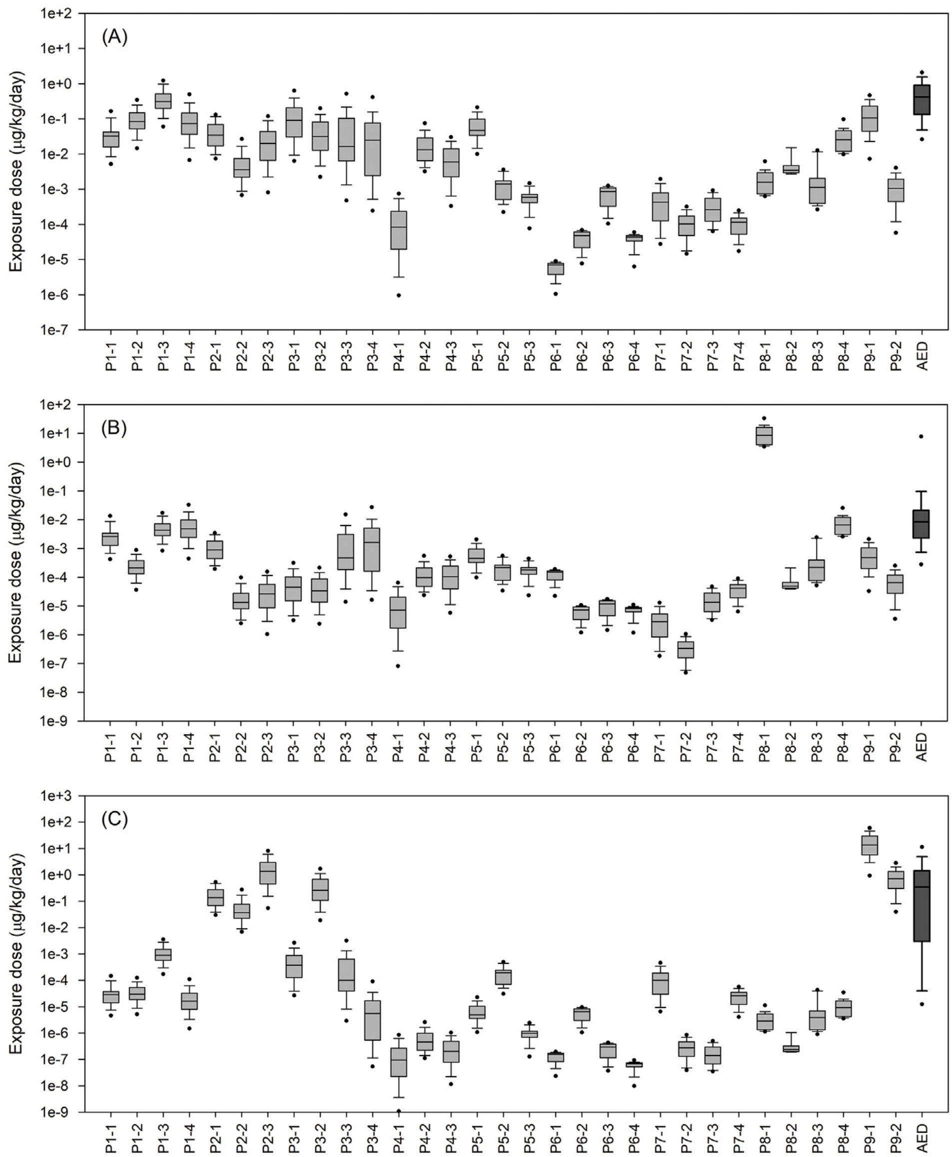

Fig. 2. Exposure dose (μg/kg/day) from the use of cosmetic products to (a) di(2-ethylhexyl) phthalate (DEHP), (b) di-n-butyl phthalate (DnBP), and (c) diethyl phthalate (DEP). Each grey box represents one cosmetic product (P1-1: skin toner, P1-2: face lotion, P1-3: face cream, P1-4: facial sunscreen, P2-1: hair dye, P2-2: hair treatment, P2-3: hair styling, P3-1: body lotion, P3-2: hand cream P3-3: deodorant, P3-4: body sunscreen, P4-1: hand wash, P4-2: face cleanser, P4-3: shaving cream, P5-1: foundation, P5-2: makeup base/primer, P5-3: pact/powder, P6-1: eyeliner, P6-2: eyeshadow, P6-3: mascara, P6-4: eyebrow, P7-1: lip balm, P7-2: lip tint, P7-3: lip gloss, P7-4: lipstick, P8-1: nail polish, P8-2: gel nail polish, P8-3: nail strengthener, P8-4: nail remover, P9-1: shower cologne, P9-2: perfume), with the dark grey box indicating the aggregate exposure dose (AED) based on individual cosmetic product use and exposure factors. The horizontal lines show the median, the boxes show the quartiles, the whisker caps show the 10th and 90th percentile values, with the 5th and 95th percentiles plotted as dots.

DEHP concentration in the five categories (nail care, skin care, body care, fragrance, and base makeup products) exceeded 10 μg/g. For DnBP, the maximum concentration (46.34 mg/g) was found in nail polish in the nail care products category. For DEP, the maximum concentration (1.58 mg/g) was found in shower cologne within the fragrance products category, and the median value was highest in hair care products. In the other categories, both the detection frequency and maximum DEP concentration were low.

3.4. Receptor-based aggregate exposure assessment

Fig. 2 shows the distribution of the exposure dose (μg/kg/day) of the three phthalates for 31 cosmetic products determined using the receptor-based approach with the maximum phthalate concentrations, daily mass, and body weight of the product users. The average aggregate exposures of the Korean population to phthalates in cosmetic products were 0.68 ± 0.87, 1.08 ± 5.71, and 2.47 ± 9.05 μg/kg/day for DEHP, DnBP, and DEP, respectively. The 95th percentiles (P95) of the AED were 2.06, 7.67, and 11.04 μg/kg/day for DEHP, DnBP, and DEP, respectively.

For DEHP, face cream had the highest average exposure dose (0.44 ± 0.43 μg/kg/day), followed by body lotion (0.18 ± 0.26 μg/kg/day) and shower cologne (0.16 ± 0.17 μg/kg/day). Overall, the exposure dose was higher for the products applied to a large surface area of the body, such as the whole face, hair, and body, than for eye and lip makeup products that were applied to a smaller surface area. For DnBP, nail polish had the highest average exposure dose (12.29 ± 15.45 μg/kg/day), followed by facial sunscreen (0.01 ± 0.03 μg/kg/day) and nail polish remover (0.01 ± 0.01 μg/kg/day). For DEP, shower cologne had the highest average exposure dose (20.73 ± 21.3 μg/kg/day), followed by hair styling products (2.71 ± 5.52 μg/kg/day) and perfume (0.96 ± 0.96 μg/kg/day).

Table 3 shows the number of cosmetics used and the AED for the 10 gender–age population groups. The highest AEDs were found for the female and young groups. The difference by gender was significant for DEHP, DnBP, and DEP ($p < 0.001$); however, the difference by age was significant only for DEP. The 19–29-year-old female group had the highest average AEDs for DEHP and DEP and the second highest AED for DnBP among the 10 gender-age groups, likely because they used the largest number of cosmetic products.

3.5. Product contribution for the AED_r

The contributions of cosmetic products to AED differed among

Table 3
Number of cosmetic products used and aggregate exposure dose (AED, μg/kg/day) by gender–age population group (mean ± SD).

	Age group	Number of products used	AED (μg/kg/day)		
			DEHP	DnBP	DEP
Female	19–29	14.5 ± 3.9	1.23 ± 1.36	2.68 ± 7.15	8.73 ± 24.33
	30–39	13.0 ± 3.9	1.16 ± 1.09	2.74 ± 6.06	3.61 ± 8.08
	40–49	12.7 ± 3.3	1.22 ± 1.07	1.92 ± 5.93	3.00 ± 7.11
	50–59	11.9 ± 2.8	1.11 ± 0.77	1.56 ± 5.03	2.22 ± 5.44
	60+	11.1 ± 2.6	0.90 ± 0.52	2.26 ± 14.90	2.11 ± 5.37
	Pooled	12.7 ± 3.5	1.14 ± 1.02	2.20 ± 8.00	3.89 ± 12.34
Male	19–29	5.0 ± 1.4	0.31 ± 0.41	0.01 ± 0.01	1.55 ± 3.77
	30–39	5.2 ± 2.4	0.28 ± 0.30	0.03 ± 0.24	1.84 ± 4.53
	40–49	4.3 ± 2.0	0.19 ± 0.20	0.00 ± 0.01	1.06 ± 2.94
	50–59	4.0 ± 2.1	0.22 ± 0.36	0.00 ± 0.01	0.57 ± 1.77
	60+	3.8 ± 1.6	0.19 ± 0.23	0.00 ± 0.01	0.22 ± 0.49
	Pooled	4.5 ± 2.2	0.24 ± 0.32	0.01 ± 0.11	1.09 ± 3.16
Pooled	19–29	9.5 ± 5.8	0.75 ± 1.08	1.28 ± 5.10	4.97 ± 17.35
	30–39	9.0 ± 5.1	0.71 ± 0.90	1.35 ± 4.44	2.70 ± 6.55
	40–49	8.4 ± 5.0	0.70 ± 0.92	0.95 ± 4.27	2.02 ± 5.49
	50–59	7.9 ± 4.7	0.66 ± 0.75	0.77 ± 3.61	1.39 ± 4.10
	60+	7.5 ± 4.3	0.55 ± 0.53	1.15 ± 10.64	1.18 ± 3.94
	Pooled	8.5 ± 5.1	0.68 ± 0.87	1.08 ± 5.71	2.47 ± 9.05

phthalates. Fig. 3 shows the pattern of product contributions by population group. For the DEHP exposure of the entire population, skin care products, body care products, and cleanser products contributed 66.8, 20.9, and 4.5%, respectively. As age increased, the contribution to DEHP exposure from skin care and hair care products increased, while that of body care products decreased. For the DnBP exposure of the entire population, nail care products contributed 98.6%, and skin care products contributed 1.2%. The contribution to DnBP exposure from nail care products was consistent. For the DEP exposure of the entire population, fragrance products, hair care products, and body care products contributed 66.3, 23.3, and 10.3%, respectively. The contribution to DEP exposure from hair care products increased with age. The contribution to DEP exposure from fragrance products was higher in the female group than in the male group.

3.6. Comparison of AED_r and AED_p

Fig. 4 compares AED values determined by the receptor-based exposure method (AED_r) and by the product-based exposure method (AED_p). For all three phthalates, the increase in AED_p was steeper than that in AED_r. The AED_r was lower than the AED_p at low percentiles, but was similar or higher than the AED_p at high percentiles. At P1, i.e., the lowest value, AED_r values were one order of magnitude lower than those of AED_p for DEHP, and four orders of magnitude lower for DnBP and DEP. At P50, i.e., the median value, DEHP had similar AED_r and AED_p values, and AED_r was slightly higher than AED_p in the percentile range of P56 to P95. However, AED_r values at P50 were lower than AED_p values by two orders of magnitude for DnBP and by one order of magnitude for DEP. DnBP and DEP had a higher AED_r than AED_p above P91 and P90. At P100, i.e., the highest value, DEHP had a slightly lower AED_r than AED_p, whereas AED_r values were one order of magnitude higher than AED_p values for DnBP and DEP.

4. Discussions

4.1. Exposure factors

Korean national exposure factors for multiple cosmetic products were collected in this study. As concern over chemical exposure through cosmetic products has increased, several large-scale exposure factor surveys have been conducted in the Netherlands (Biesterbos et al., 2013), France (Dornic et al., 2017; Ficheux et al., 2015, 2016) and the United States (Loretz et al., 2005, 2006, 2008; Wu et al., 2010). The consumption patterns of cosmetics can be strongly influenced by national, ethnic, and cultural backgrounds. Therefore, it is not appropriate to apply European and American exposure factors the estimate the exposure of the Korean population.

This study derived nationally representative exposure factors for Korea. The subjects were adults (over 19 years old) and were sampled considering gender, age, and regional distribution. The use rates and exposure factors of 31 cosmetic products sorted into nine categories were derived from a face-to-face survey. Most of the exposure factors used in recent Korean studies (Jung et al., 2018; Park et al., 2018) were obtained through online questionnaire surveys. Although online surveys are simple and they make it easy to obtain a large number of responses, the sample can be biased and less representative. The advantages of a face-to-face interview include the selection of an unbiased representative sample of subjects and enhanced accuracy of questionnaire responses. Subjects in this study had a similar use frequency to Americans and Europeans, but used lesser amounts of cosmetic products, overall.

The exposure factors of many cosmetic products were the same. For many non-makeup products, e.g., skin care products, the use frequency was similar at the median, 75th percentile, and 95th percentile. Variations in the amount of product used were also very small. When the daily mass of products was derived from the use frequency and amount, the variation in the daily mass of non-makeup products was found to be very small. Therefore, the daily mass of many non-makeup products did not differ significantly with demographic factors. Makeup cosmetics are mainly used by females. The daily mass of makeup cosmetics differed significantly between females and males, as males do not tend to use these products. However, the variation in the daily mass of non-makeup products used by females was also very small.

The exposure factor database included users and non-users of multiple representative cosmetic products. Exposure factors for the simultaneous use of multiple products are critical for receptor-based aggregate exposure assessments. Aggregate exposure was therefore based on the actual use of cosmetic products. The use pattern of cosmetic products was very different for specific populations. For example, makeup cosmetics were mainly used by females. Because the exposure factor survey collected use patterns and exposure factors of products used at the same time, the data could be applied to receptor-based aggregate exposure assessments.

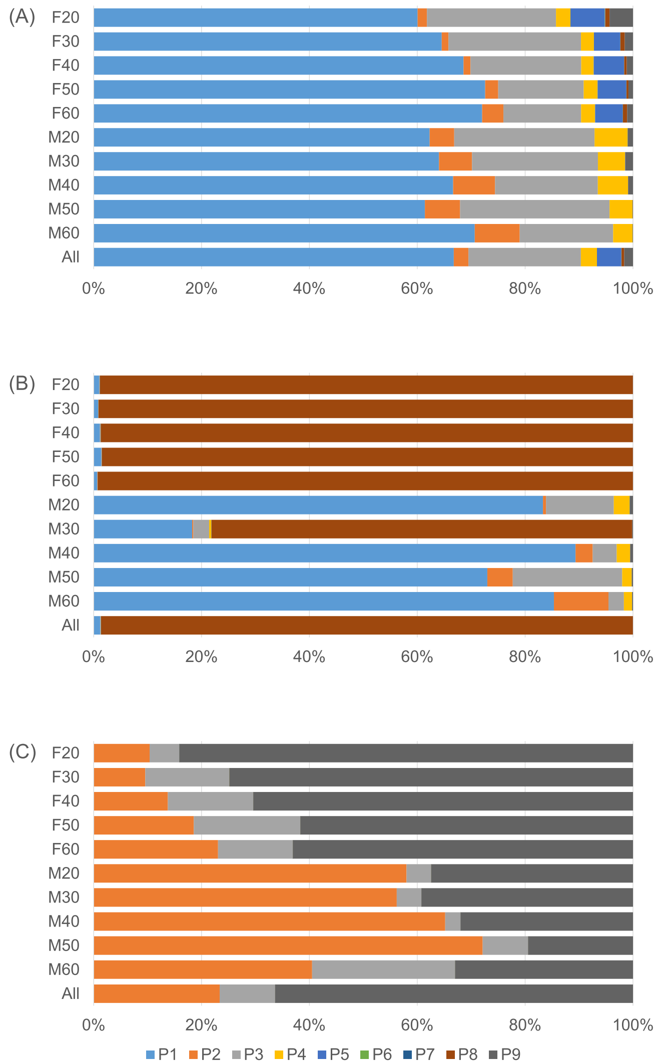

Fig. 3. The contribution of different products to the receptor-based aggregate exposure dose (AED) of (a) di(2-ethylhexyl)phthalate (DEHP), (b) di-n-butyl phthalate (DnBP), and (c) diethyl phthalate (DEP) by population group. Each colored bar represents one cosmetic category (P1: skin care products; P2: hair care products; P3: body care products; P4: cleanser products; P5: base makeup products; P6: eye makeup products; P7: lip makeup products; P8: nail care products; P9: fragrance products).

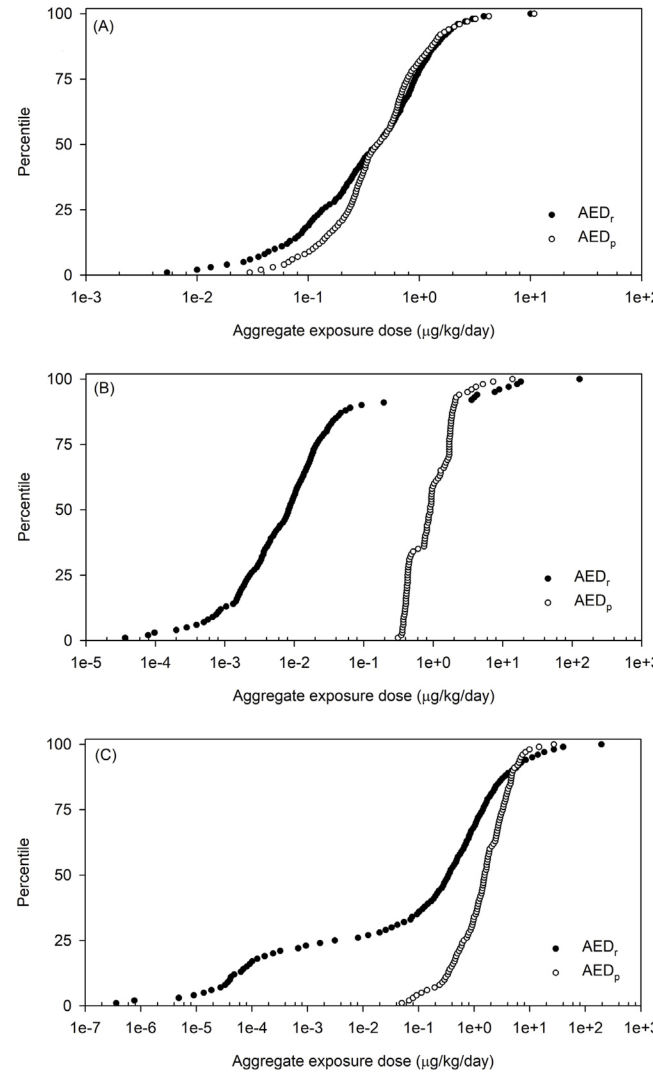

Fig. 4. Comparison of the aggregate exposure dose (AED) estimated by the receptor-based exposure method (AED_r) and product-based exposure method (AED_p) for (a) di(2-ethylhexyl)phthalate (DEHP), (b) di-n-butyl phthalate (DnBP), and (c) diethyl phthalate (DEP). Each black dot represents 1 percentile of the AED based on individuals' actual use of a product and the exposure factor. Each white dot represents a 1 percentile value of AED based on the exposure dose of each product consumed and the use rate of the population.

4.2. Chemical concentrations

Phthalates in cosmetic products are used as additives, stabilizers, and fixing agents. DEHP is used for plasticizing or softening other ingredients. DnBP is used as a coating agent to reduce cracks in cosmetic products such as nail polish. DEP is used as a solvent and fixative in fragrances (US FDA, 2018). Due to their widespread use, phthalates in cosmetic products have been reported in Korea (Koo and Lee, 2004), Canada (Koniecki et al., 2011), the United States (Guo and Kannan, 2013), China (Guo et al., 2014) and Saudi Arabia (Al-Saleh and Elkhatib, 2016).

This study found a high frequency of DnBP at high concentrations in coating products, such as nail care products. Although DEP was frequently detected in fragrance products (8 of 10 products) at high concentrations, the overall detection rate (41 of 214 products, 19.2%) was the lowest of the three phthalates. DEHP was the most frequently detected (143 of 214 products, 66.8%) phthalate in the cosmetic products investigated in this study. This differed from previous studies in which DEP was detected at the highest frequency (Guo and Kannan, 2013; Koniecki et al., 2011). However, the maximum DEHP concentration in cosmetic products was relatively low compared to the maximum DnBP and DEP concentrations.

4.3. Aggregate exposure assessment

Initially, estimates of the aggregate exposure to chemicals in consumer products were made by measuring the annual volume of chemicals used over a specific geographic area. This approach provides a crude estimate. The aggregate consumer exposure from each product, represented by the product-based method in this study, is a more realistic estimation method than is determining environmental exposure (Cadby et al., 2002). Measurement of product-based aggregation requires data on the use rate of each product, the product exposure factor, and the concentration of its chemical ingredients. However, the product-based aggregate exposure approach can provide an inaccurate estimate. When the use rate of a single product is employed, the population that rarely uses products or that uses many kinds of products cannot be included in the product-based aggregate exposure distribution.

The receptor-based aggregate exposure method used in this study can provide a more accurate measure because it uses simultaneous information on use in nationally representative samples. In this study, the simultaneous use patterns for 31 cosmetic products included actual co-use and non-use information. The daily mass amount derived from the exposure factors clearly differed according to use or non-use. Nationally representative study samples that considered gender, age, and regional distribution provided an accurate estimate of exposure among the Korean population. Exposure factors for multiple cosmetic products were collected simultaneously with use patterns. The database used in the study had a critical impact on the receptor-based aggregate exposure estimation of common ingredients in cosmetics and on product contribution to the AED.

The distributions of AED_p and AED_r clearly differed for DnBP and DEP, whereas the AED_p and AED_r distributions for DEHP were similar. The population averages of the AED_r values for DnBP and DEP were lower than those obtained using the product-based method. Cowan-Ellsberry and Robison (2009) suggested an aggregate exposure estimation method using a female exposure group based on the use and non-use of nine consumer products. Their refined model partially considered co-use patterns and estimated 36–56% lower aggregate exposure than did a simple product exposure addition method. However, the 95th percentile of the AED_r was higher than the AED_p for DnBP and DEP.

The AED_p for the three phthalates in cosmetic products displayed less variation than did the AED_r. In the AED_p, the use rate of each product was applied. However, aggregate exposure is associated with the simultaneous use of multiple products. This method did not consider those who rarely use products or those who use many kinds of products. In addition, the exposure factors of cosmetic products had a narrow distribution of values, with a small range. The smaller range of the AED_p for cosmetic products might be related to the aggregate exposure's being derived from such narrow distributions of exposure factors.

The population for which AED_r was higher than AED_p comprised mostly female and younger subjects. The contact points of the AED_r and AED_p distributions were the 91st percentile for DnBP and the 90^{th} percentile for DEP. Of the 90 subjects above the 91st percentile for the DnBP AED_r, 89 were females and 53 were aged 19–39. Of the 100 subjects above the 90^{th} percentile of the DEP AED_r, 71 were females and 58 were aged 19–39. The difference between the AED_r and AED_p ratios among the young female group were larger than those for the senior male group for all three phthalates (See Table S5).

The receptor-based aggregate exposure was previously calculated for Europeans using a person-oriented exposure model. The probabilistic aggregate consumer exposure model (PACEM) is based on exposure factors for 32 personal care and cosmetic products obtained from a survey of 512 Dutch adults (Delmaar et al., 2015). The PACEM model includes personal care products that were not considered in this study, such as shower gel, shampoo, conditioner, and toothpaste. The PACEM model used a DEP concentration from the available literature. The dermal absorption factor for the different products (range from 0.02 to 1) was used in the exposure dose calculation. Although the target products and estimation method were not identical for the different studies, the AED trend by gender was similar in Korean and European populations. The 95th percentile aggregate DEP dose for the Korean population was 3.46 times higher in females than in males. The 95th percentile aggregate DEP dose for the European population was 1.12 times higher for females than males.

The highest exposure group estimated by the receptor-based approach was the 19–29-year-old female group. This group was exposed to 6.4 times, 660.5 times, and 39.7 times higher concentrations of DEHP, DnBP, and DEP, respectively, than was the male group aged 60 + years, which had the lowest exposure. The number of cosmetic products used by the 19–29-year-old female group was 3.9 times greater that used by the 60 + male group. The population that co-used many different products was also the high exposure population. Although current regulations are based on exposure from a single product, aggregate exposure should be considered in the future. If the aggregate exposure is applied for the regulation of cosmetics, particular attention should be given to the exposure status and patterns of the young female group.

4.4. Product contribution

The cosmetic products that made the largest contributions to the total exposure differed among the three phthalates. Aggregate DEHP doses were influenced by relatively more cosmetic products than were aggregate DnBP and DEP doses. DEHP was present in low concentrations in most cosmetic product categories. All product categories contributed to the aggregate DEHP doses. Nail care products were the major contributor to the aggregate DnBP doses. Fragrance products, hair care products, and body care products were the major contributors to aggregate DEP doses.

The products contributing the majority of DnBP among the 29–39-year-old male group were different from those responsible for exposure in male groups of other ages. Of the 509 male subjects, only one person answered that he used both nail polish and nail strengthener. As a result, nail care products contributed 78.0% of the DnBP AED for the 29–39-year-old male group. Excluding this respondent, the contribution of skin care products increased from 18.3 to 83.1%, and the contribution of body care products increased from 2.9 to 13.4%, similar to the contributions for the other male groups. The DnBP concentration in the nail care products investigated in this study was overwhelmingly high, with a maximum concentration of (46,337.68 μg/g), and the second (1.88 μg/g) and third (1.53 μg/g) highest DnBP concentrations were also detected in nail care products. Therefore, there would be a similarly high contribution from nail care products to the DnBP AED nail care product users regardless of the nail care product's DnBP concentration. The distribution of DnBP AED was determined by nail care product use. Specific product management is required when certain cosmetics contain particularly high levels of certain chemicals.

Cosmetics were usually used at a regular frequency, typically once or twice a day. The variation among product users in daily mass used was small. Demographic factors had no effect on the exposure dose of the product. The number of cosmetics used and the use of specific cosmetic products containing high concentrations of phthalates were one of the main characteristics of the high exposure group. To obtain an accurate receptor-based aggregate exposure assessment of cosmetic products, it is important to know which cosmetic products are used simultaneously. Furthermore, it is necessary to develop a cosmetics co-use exposure scenario by population group.

4.5. Limitations

This study estimated the aggregate exposure to three phthalates from the use of 31 cosmetic products. The exposure factors of this study might have potential error because all the survey responses were considered true. The three phthalates may also be included in other consumer products. In particular, personal care products such as shampoo, toothpaste, and body cleanser were not considered in this study. The diet sources had larger contribution than non-diet sources to phthalate exposure (Giovanoulis et al., 2018; Martínez et al., 2018; Romano et al., 2019). Therefore, the results could have underestimated the aggregate exposure of the three phthalates in the Korean population. For the more accurate receptor-based aggregate exposure assessment, diet and non-diet sources should be considered.

The AED of cosmetic products might have been overestimated because the maximum concentration in the cosmetic product categories was used for aggregate exposure estimation. The maximum concentrations used for each product in this study may have been overestimated. The phthalate concentrations in various products would likely be lower than the maximum values used in this study. For more accurate assessment, the actual concentrations in the particular cosmetics used should be applied. However, the 214 products analyzed did not include all of the products that survey respondents actually used.

The AED of cosmetic products might be overestimated because this study assumed a skin absorption rate of 100% for all three phthalates. Although there have been experimental studies at the cellular level regarding the rate of skin absorption of single phthalates (Koo and Lee, 2004), the absorption of the substances contained in actual products has not yet been assessed. Although hair follicles are the main location of DEHP absorption, and they have been the focus of previous studies (Pan et al., 2014), it is possible that the absorption rate via other body parts could also be significant. Due to the lack of specific skin absorption rate information by product and body part, a conservative skin absorption rate was used in this study.

5. Conclusions

The DEHP, DnBP, and DEP AED values for 31 cosmetic products were estimated for the Korean population. The receptor-based aggregate exposure assessment method would be used to determine high exposure groups. The product-based aggregate exposure assessment method underestimated the high exposure group but overestimated the average exposure for DnBP and DEP. Further studies needed to be confirm whether a similar phenomenon occurred for other chemicals. The AED_r was significantly different by age and gender. The high exposure group for phthalates in cosmetics was young females because they used a large number of cosmetic products. The receptor-based AED for DEHP, DnBP, and DEP could identify the contribution of cosmetic products.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.031.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2019.03.031.

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