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臺灣國人尿液中鄰苯二甲酸酯類及其替代品之代謝產物基線值之建立：2019臺灣全國代表性樣本及其分析

Taiwanese Reference Values for Urinary Metabolites of Phthalate Esters and Substitutes Derived from Nationwide Representative Samples of Taiwan Human Biological Monitoring in 2019

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本論文係陳冠逸君（R10852026）在國立臺灣大學環境與職業健康科學研究所完成之碩士學位論文，於民國 112 年 06 月 01 日承下列考試委員審查通過及口試及格，特此證明

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中文摘要

自 2011 年發生食品鄰苯二甲酸鹽事件後中，di-(2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate (DiNP) 被非法添加到食品和藥物中，臺灣民眾開始關注食品安全，在這件事發生後，儘管使用上已有諸多政策的相關限制，但臺灣民眾仍會接觸到一定程度的鄰苯二甲酸酯類。DEHP 和 DiNP 作為廣泛使用的塑化劑，被諸多研究證實是內分泌干擾物質的一種，對人類的生殖、內分泌系統具有毒理作用。

許多國家多年來都持續進行著全國性的監測調查，像從 1960 年代初開始的美國，開始了名為 National Health and Nutrition Examination Survey (NHANES)；1985 年在德國，German Environmental Survey (GerES) 開始在西德進行生物監測研究；韓國於 2005 年也開始了 Korean National Environmental Health Survey (KoNEHS)，旨在製定和支持環境相關的政策；最後是加拿大，他們建立了 Canadian Health Measures Survey (CHMS)，從 2007 年開始收集人體生物監測數據。但是，我們國家卻遲遲沒有進行全國性的人體生物監測調查，來收集有關鄰苯二甲酸酯類的代謝產物及其替代產品之暴露水平與濃度基線值的資料。

我們旨在建立一個具有全國代表性的人體生物監測研究，並利用此資料建立鄰苯二甲酸酯類及其替代品的尿中代謝產物，有關臺灣國人的濃度基線值與其分布狀況。我們從 2019 年進行的臺灣國民營養健康調查中招募了 1748 名 7 歲及以上的參與者，方法是使用 PPS (probability proportional to size)法抽出村里 PSU (Primary sampling unit)進行分層多階段集束抽樣，覆蓋臺灣 20 個城市或縣。每個鄉鎮和市區依人口密度和都市化程度各分 2 小層。我們收集了參與者的尿液和血液，並同時收集了有關生活環境和飲食習慣的問卷調查。於尿液檢體的分析上使用超高效液相色譜-串聯式質譜儀測定每個參與者尿液樣本中 12 種不同鄰苯二甲酸酯類及其替代品之代謝產物(MEHP、MECPP、MiBP、MnBP、MEP、MHINP、MCINP、MBzP、MnOP、oxo-MPHP、OH-MINCH、MECPTP)。我們將臺灣國人之鄰苯二甲酸酯及其替代品之代謝產物分佈的結果與其他國家代表性樣本進行了比較，提供

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了對各種健康相關主題的國家級估計，在 2019 年的數據中我們發現，大部分的代謝產物濃度在低年齡層組別(7-12 歲)都顯著高於其他年齡層組別(除 MEP、MnOP、MBzP)，且在與其他國家進行比較時，同時也發現我國在與他國全國性代表資料比較之下，我們國民在 MEHP、MECPP、MnBP、MiBP 幾種代謝產物之濃度仍明顯高於其他國家，而在替代產物 oxo-MPHP、OH-MINCH、MECPTP 的濃度則明顯低於其他過家的狀況出現。我們同時使用國人的鄰苯二甲酸酯類及其替代品之代謝產物之基線值與 Human biomonitoring initiative (HBM4EU)所公佈的 HBM guidance values (HBM-GVs)及 HBM-I Value 進行比較，其中發現我國國民在兒童組於 MnBP、MiBP 兩組均有出現超標狀況，超標情形分別為 0.42%、0.83%，利用外插法推估至全國人民時則有約 5892 至 11784 名兒童有超過健康風險指標值的狀況；而在青少年及成人組的部分，則是發現 MnBP、MiBP 及 oxo-MPHP 等三組有出現超標情形，其比例分別為 0.13%、0.07%、0.20%，利用外插法推估至全國人民時則有約 13791 至 41373 名國人有超過健康風險指標值的狀況。由於監測資料我們得知目前我們鄰苯二甲酸酯類及其替代品的暴露水平依然有高於其他國家且高於健康風險指標值的情形存在，且在塑化劑相關政策管控上仍尚未進行替代品之管制，因此預計持續使用這一項具有全國代表性的人體生物監測研究，以評估臺灣國人對於這些內分泌干擾物質的暴露水平，用以確保我們臺灣民眾每一階段鄰苯二甲酸酯類及其替代品的暴露水平是處在一個安全的生活環境之中。

關鍵詞：鄰苯二甲酸酯類及其替代產品，人體生物監測，尿液代謝產物，生物標誌物，國民營養健康調查，全國代表性樣本，基線值

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Abstract

Since 2011, there was an incident involving phthalate-tainted food, Taiwanese people have become concerned about food safety. Although after this incident happened, people in Taiwan are still being exposed to certain levels of phthalates esters. At that incident, di-(2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate (DiNP) were illegally added to foodstuffs and medications. DEHP and DiNP, as widespread plasticizers, are considered endocrine disrupting chemicals (EDCs) with main toxicological effects on reproductive and metabolic systems. We like to start a nationwide Human biomonitoring (HBM) studies to evaluate the background exposure levels of these EDCs in Taiwan.

Nationwide monitoring surveys have been conducted in many countries. Like the United States beginning in the early 1960s, which call the National Health and Nutrition Examination Survey (NHANES); and in 1985 in Germany, the German Environmental Survey (GerES) began biomonitoring in West Germany; other like the Korea, they also started their Korean National Environmental Health Survey (KoNEHS), which began in 2005 to establish and support environmental policies; and the last but not the least is Canada, they conducted Canadian Health Measures Survey (CHMS) beginning to collect human biomonitoring data in 2007. However, there is no nationwide human biomonitoring survey had been conducted to gather information on levels or reference values (RVs) of phthalates in the Taiwanese population in recent years.

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We aimed to establish the urinary levels and RVs of phthalate metabolites and identify exposure characteristics among Taiwan's population. We enrolled 1748 participants 7 years of age and older from the Nutrition and Health Survey in Taiwan (NAHSIT) conducted in 2019 by using probability proportional to size (PPS) and primary sampling unit (PSU) sampling covering 20 cities or counties of Taiwan. Each township and city district were classified into one of two groups according to its population density and urbanization level. We collected participant's urine and blood, and did the environmental and lifestyle questionnaires. Levels of 12 different phthalate metabolites (MEHP, MECPP, MiBP, MnBP, MEP, MHINP, MCINP, MBzP, MnOP, oxo-MPHP, OH-MINCH, MECPTP) in each participant's urine samples were determined using Ultra Performance Liquid Chromatography-tandem mass spectrometry (UPLC-MS/MS) for analysis. The results of phthalate esters distribution in Taiwan were compared with other national representative samples that provide national estimates on various health-related topics. Data from 2019 show that concentrations of most metabolites in younger age groups (7–12 years) are significantly higher than in other age groups (except MEP, MnOP and MBzP). According to representative data from other countries, the concentrations of metabolites of MEHP, MECPP, MnBP, and MiBP in our country are still significantly higher than those of other countries; while the concentrations of alternative products, oxo-MPHP, OH-MINCH and MECPTP are significantly lower than others. And we also used our RVs of urinary

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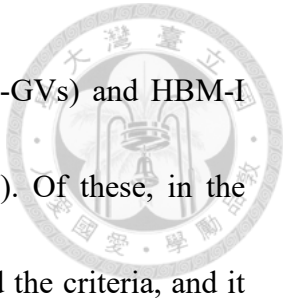

phthalate metabolites compared with HBM guidance values (HBM-GVs) and HBM-I Value announced from Human biomonitoring initiative (HBM4EU). Of these, in the children group, both the MnBP group and the MiBP group exceeded the criteria, and it was found that the cases exceeding the criteria were 0.42% and 0.83%, respectively. Using extrapolation to estimate the national population, there were approximately 5,892 to 11,784 children who exceeded the threshold which is the status of the risk index value. Among adolescents and adults, three groups were found to exceed the norm: MnBP, MiBP, and Oxo-MPHP, at rates of 0.13%, 0.07%, and 0.20%, respectively. Using extrapolation to estimate the national population that about 13,791 to 41,373 people are above the health risk index values. Monitoring data shows that our exposure to phthalates remains higher than in other countries, and some phthalates and their substitutes were above health risk indicators. Our political restrictions on plasticizers substitutes have not yet been implemented well. Therefore, this national representative human biomonitoring study will continue to be conducted to ensure that Taiwan's phthalates exposure level every year are safe and make some recommendation to our government. In order to make sure our Taiwanese general population keep in a safe living environment.

Keywords: phthalate esters, human biomonitoring, urine, biomarker, NAHSIT, nationwide sample, reference values

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Chapter 1. Introduction

Plastics that come in contact with food are part of our daily lives. Microplastics are tiny plastic particles that come into contact with various chemicals, and phthalates can enter the intestines of mice through microplastics and cause worse side effects (1). Since 2011, there have been cases of phthalate-contaminated food, in which di-(2-ethylhexyl) phthalate (DEHP) and di-isononyl phthalate (DiNP) were illegally added to food and medicines (2). DEHP and DiNP, as widespread plasticizers, are considered endocrine disrupting chemicals (EDCs) with main toxicological effects on reproductive and metabolic systems. After that phthalate-tainted food incident, Taiwanese people have become concerned about food safety.

Phthalates are regulated and banned internationally due to their toxicity. However, industry uses and discovers other chain lengths or same molecular isomers and other alternative chemicals as substitutes (3). These alternative chemicals are not yet being explored and surveyed their toxicity, exposure distribution and health impacts. Biomonitoring approach allows us to investigate the effects of these chemicals on the human body. Through biomonitoring techniques, possible links between chemical concentrations and environmental factors can be established. Knowing possible sources of exposure and protecting the general public from health risks.

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1.1 Phthalate esters (PAEs)

1.1.1 PAEs

Phthalates are a group of chemicals found in many consumer products, including personal care products, fast-food consumption, cosmetics, plastic products, toys, furnishings, and ready-to-eat and takeout (5). Phthalates are organic synthetic chemicals that are consumed in millions of tons annually worldwide. Phthalates add flexibility to rigid materials such as polyvinyl chloride (PVC) and also act as lubricants, plasticizers, or deodorants (2, 4, 6).

Phthalates are divided into two groups based on their weight. One is the low molecular weight (LMW) groups such as butyl benzyl phthalate (BBzP), diethyl phthalate (DEP), di-isobutyl phthalate (DiBP), and di-n-butyl phthalate (DnBP). Another group is the high molecular weight (HMW) groups such as DEHP, DiNP, and mixtures of di-n-octyl phthalates (DnOP). Phthalates are well known for their use as plasticizers in PVC materials like food packaging, flooring and medical devices (7, 8).

Phthalates are present in detectable amounts in a variety of environments (air, water, soil, sediments) worldwide. DEHP is the most important phthalate pollutant in the environment (9). The rate of photolysis and hydrolysis of these contaminants is very slow under natural conditions. Previous studies have shown that the water-soluble photolytic half-life of BBzP exceeds 100 days, the phthalate hydrolyzes at a negligible rate at neutral

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pH, and the half-life of dimethyl phthalate (DMP) ranged from about 3 years to 2000 Year of DEHP (10, 11). Removal and degradation of PAEs by abiotic processes under natural conditions such as hydrolysis and photolysis are very slow and insignificant (12, 13). Microbial degradation of PAEs is considered one of the major pathways for environmental degradation of these contaminants (14).

1.1.2 PAEs substitutes

In parallel with the phase-out of some phthalates which containing endocrine disruptors, di-(2-propylheptyl) phthalate (DPHP), di-2-ethylhexyl terephthalate (DEHTP) and di-iso-nonyl-cyclohexane-1,2-dicarboxylate (DINCH) these new substances have been investigated and introduced as a replacement for DEHP and other high molecular weight phthalates (15, 16). The production and use of the plasticizers Hexamoll® DINCH and DPHP began in the early 2000s in both chemicals increased after the substance was commercialized. As replacements for HMW restricted phthalates (3).

DINCH and DEHTP are structurally similar to phthalates and are similarly metabolized and excreted. DINCH and DEHTP are not only used as replacement plasticizers for reproductively toxic HMW phthalates such as DEHP, but also as substitute plasticizers for DnBP, DiBP and BBzP. It is especially used in regulated or high exposure potential products such as toys, food contact materials and medical applications (17, 18, 19).

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1.1.3 Pathways and metabolism

Even though most of these compounds have been phased out or restricted, PAEs is still found in air, dust, food, and hand wipes. Ingestion appears to be the most important route of exposure, followed by inhalation and dust ingestion (20). Once PAEs enter the human body, they are rapidly metabolized to their respective hydrolyzed and oxidized monoesters, which are further excreted in the urine and feces after partial glucuronidation (21).

Phthalates have short half-lives in the human body and are rapidly excreted in the urine as monoester metabolites. The half-life of phthalates in the human body (plasma and urine) is less than 24 hours, and after metabolism monoesters of phthalates bind glucuronides or sulfates and are excreted in the urine not more than 48 hours (17; 22). Metabolites are useful biomarkers of human exposure to the parent compound. Each parent phthalate can be detected in varying numbers of its respective monoester as primary metabolite and oxidative metabolite as secondary metabolite (8). Like DEHP as the parent compound, its primary metabolite is Mono 2-ethylhexyl phthalate (MEHP) and its secondary metabolites are Mono 2-ethyl-5-hydroxy-hexyl phthalate (MEHHP), Mono 2-ethyl-5-oxo-hexyl phthalate (MEOHP) and Mono 2-ethyl-5-carboxy-pentyl phthalate (MECPP) (23).

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1.1.4 Health effects

The available toxicological data indicate genotoxicity, cytotoxicity, and embryotoxicity of certain PAEs, especially DEHP, providing strong evidence that PAEs have unique toxic mechanisms in vivo. There was strong evidence of an association between exposure to PAEs and reproductive outcomes in men. This was primarily based on studies of anogenital distance, semen parameters, and testosterone on DEHP, semen parameters and time to pregnancy on DBP (24, 25, 26). Past studies have also shown that childhood exposure to phthalates may increase the risk of allergic sensitization and atopic disease. Several results indicate a sexual relationship between phthalate metabolites and thyroid hormones. Other studies suggest that a child's co-exposure to DEHP and other phthalates is negatively associated with lung function (27, 28, 29).

Also, according to the current state of knowledge, current toxicological data indicated that phthalate substitutes such as DINCH are neither reproductive toxic nor endocrine disruptors. However, adverse health effects, namely thyroid hyperplasia and nephrotoxicity, were observed in rats at relatively high doses. DPHP is also being used as an alternative to DEHP and DiNP with increasing global consumption. No developmental or testicular effects were observed in rats, but adverse thyroid, pituitary and adrenal gland effects were observed (17, 30, 31). For DEHTP, toxicological animal studies have shown no associated endocrine disrupting potential, reproductive toxic effects, or (or weak)

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peroxisome proliferation potential. The most sensitive endpoints are retinal and nasal turbinate effects (3, 32, 33).

1.2 Human biological monitoring (HBM)

1.2.1 HBM

Human biological monitoring has become an important tool in environmental and occupational medicine for assessing levels of internal exposure to contaminants intake from the general and occupational environment. Generally, HBM is used to assess levels of internal exposure to hazardous substances by measuring the concentration of the substance or its metabolites in blood, urine, or other human biological material suitable for chemical analysis (34).

Nationwide human biomonitoring surveys have been conducted in many countries. The National Health and Nutrition Examination Survey (NHANES) has been conducted several times in the United States since the early 1960s; in 1985, the German Environmental Survey (GerES) started biomonitoring in West Germany; the Korea National Environmental Health Survey (KoNEHS) started in 2005 to formulate and support environmental policies; and the Canadian Health Measures Survey (CHMS) began collecting HBM data in 2007. Human biomonitoring studies have provided valuable baseline data on internal exposure to phthalates in the general population. However, the effects of phthalates vary from population to population, depending on diet

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and lifestyle. Concentrations of phthalate metabolites in the human body vary widely depending on demographic trends (35). Therefore, it is important to have your own HBM surveys in your country due to the large number of variations.

1.2.2 Reference Values (RVs)

Human biomonitoring is recognized as a measure of the internal dose of a chemical from cumulative exposure over all exposure routes. Nationwide studies can be used to determine background levels and reference levels (RVs) for environmental chemicals (such as phthalate metabolites and metals) over various time periods (36).

A reference value is intended to characterize the upper limit of the current background exposure of the general population to a particular environmental toxin at a particular point in time. RVs are derived from population studies aimed at measuring the concentration of environmental toxins in the blood, urine, or other human biomaterials (hair, teeth, milk, etc.) of subjects in the general population. The reference population should cover a representative portion of the general population and be large enough to allow assessment of the effects of relevant confounding factors on the concentration of toxins in human biomaterials (e.g., age, sex, cigarette smoking, amalgam fillings, certain diets). The 90th or 95th percentile of concentration values is usually determined from these studies and defined as the RVs (37).

If blood or urine toxin levels differ significantly between these groups, RVs can be set

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for specific groups of the general population (e.g., children and adults, women and men, nonsmokers and smokers). In addition, if the concentration of toxins in blood or urine is highly age-dependent, RVs can be established for specific age groups. It is important to emphasize that reference levels do not represent toxicologically derived biological exposure limits. Therefore, they cannot be used either on an individual basis or in the context of population studies for health-related evaluation of human biological monitoring data. The main purpose of establishing RVs is to have guideline values that can be used to identify people with increased internal exposure to defined environmental contaminants (34).

1.2.3 HBM Values

HBM values are derived from toxicological and epidemiological studies and therefore represent health-related biological exposure limits. Commission of the German Federal Environment Agency usually recommends two different HBM values:

1. HBM-I value: The concentration of an environmental toxin in a human biological material (usually blood, serum, plasma, or urine) below which there is ± according to the knowledge and judgement of the commission and with regard to the environmental toxin under consideration ± no risk for adverse health effects in individuals of the general population.

2. HBM-II value: The concentration of an environmental toxin in a human biological

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material (usually blood, serum, plasma, or urine) above which there is ± according to the knowledge and judgement of the commission and with regard to the environmental toxin under consideration ± an increased risk for adverse health effects in susceptible individuals of the general population.

According to these definitions, HBM-I values represent a kind of alarm value and HBM-II values represent a kind of action level (34).

1.2.4 HBM guidance values (HBM-GVs)

The European Human Biomonitoring Initiative (HBM4EU) is a joint effort of 30 European countries, and the European Environment Agency, co-funded by the European Commission under Horizon 2020 with the goal to improve chemical safety (38). An important result is a Europe-wide improvement and harmonization of health risk assessments after a coordinated derivation or update of health-related guidance values referring to the internal body burden.

In HBM4EU established a widely recognized methodology for the so-called HBM guidance values (HBM-GVs). These values, derived from epidemiological or toxicological data, indicate concentrations of compounds or their metabolites in biological substance where no health risk is expected according to current knowledge. The HBM4EU consortium has identified 18 substances and substance groups, including phthalates, as high priority to answer outstanding policy-relevant questions through

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targeted research (38; 40).

Derivation of HBM-GVs for selected biomarkers can be performed according to three possible options (Figure 1). The most robust derivation, and therefore the first option, is based on the relationship between human internal biomarker concentrations and adverse health effects. If human data are not available, insufficient, or unreliable, one can try to proceed according to the second option, using existing external toxicity reference value (TRV), Tolerable daily intake (TDI) set by the government, using toxicokinetic data or correlations based on exposure-internal concentration relationships set to the internal value. The third option, if the TRV is considered inadequate or is not available, the HBM-GVs can be derived based on a point of departure (POD) identified in animal experimental studies (40; 44).

The HBM-GVs for five phthalates and phthalate substitute Hexamoll® DINCH presented in Table 1. These data allowed for a direct toxicological interpretation of measured exposure biomarker levels of urinary phthalates (39, 40). HBM-GVs can be compared to RVs in national surveys to ensure the public is kept in a safe environment.

1.3 Objectives

Human biomonitoring is increasingly established around the world as a tool to inform politicians and the general public about public exposure to man-made chemicals. Although there have been incidents of phthalate-contaminated food in Taiwan, there is no

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comparison of Taiwan's phthalate exposure levels with other countries, nor a nationwide or long-term continuous survey of environmental chemicals. Therefore, it is difficult to monitor changes.

We like to start a nationwide HBM studies to evaluate the background exposure levels of these EDCs in Taiwan. We aimed to establish the urinary levels and RVs of phthalate metabolites and identify exposure characteristics among Taiwan’s population. Establishing RVs allows us to compare contaminant levels measured from individuals or populations to background exposure. RVs can also be used to monitor changes in the general population's exposure to the substance over different time periods. An individual with high levels of exposure to a substance should increase vigilance if exposure exceeds RVs 95th percentile level.

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Chapter 2. Material and Methods

2.1 Materials

The targeted twelve different phthalates are as following:

(1) Mono-2-ethylhexyl phthalate (MEHP)

(2) Mono-2-ethyl-5-carboxypentyl phthalate (MECPP)

(3) Mono-i-butyl phthalates (MiBP)

(4) Mono-n-butyl phthalates (MnBP)

(5) Mono-n-octyl phthalate (MnOP)

(6) Mono-carboxyisononyl phthalate (MCINP)

(7) Mono-hydroxyisononyl phthalate (MHINP)

(8) Mono-ethyl phthalate (MEP)

(9) Mono-benzyl phthalate (MBzP)

(10) Mono-2-propyl-6-oxo-heptyl phthalate (oxo-MPHP)

(11) Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester (OH-MINCH)

(12) Mono-2-ethyl-5-carboxypentyl Terephthalate (MECPTP)

The chemical structures and molecular weights of analytes data listed in supplement 1.

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2.2 Sample collection and storage

Our nationwide representative HBM enrolled 1748 participants 7 years of age and older from the Nutrition and Health Survey in Taiwan (NAHSIT) conducted in 2019 by using probability proportional to size (PPS) and primary sampling unit (PSU) sampling covering 20 cities or counties of Taiwan. In addition, to account for seasonal and regional effects, the 20 cities or counties were divided into five groups (Northern group included Taipei City, New Taipei City, Keelung City and Yilan County; Southern & Remote group included Tainan City, Penghu County, Chiayi City and Chiayi County; Eastern group included Hualien County, Taitung County, Pingtung County and Kaohsiung City; Western group included Taoyuan City, Miaoli County, Hsinchu City and Hsinchu County; Central group included Taichung City, Changhua County, Yunlin County and Nantou County) based on regional differences, and each group was sampled in every season. Each township and city district were classified into one of two groups based on population density and degree of urbanization. In total, 160 villages in Taiwan are expected to be visited in four years, and 40 villages are visited every year. And each PSU was extracted from each layer by the PPS method. Sampling for each age group is based on the number of demographic surveys in the current year. The household registration address of each selected PSU was randomly selected, and then interviewers were asked to copy a certain number of addresses in order of address, which became a concentration area. Interviewers

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went through these addresses written by pioneers and knocked on the doors in order to ask about their willingness to participate this research. If there is one person in the household who can respond to the questionnaire, and the target number of people in the gender and age group has not been reached, we will list it as a target person. If there is no one in the household that wants to be interviewed, or if the number of applicants has been reached, we will move on to next household and continue the interview. We collected participants' first morning urine and blood, and did the environmental and lifestyle questionnaires. The questionnaire covered demographic information (age, sex, income and education level), environmental exposure (smoking, pesticide usage and house age), lifestyle questions (diet habits and takeout frequency), and other related factors survey (disease history and medication usage).

Between March and December 2019, 1575 urine and serum samples were collected from participants aged 7 years and older. Samples were placed in cool boxes with dry ice immediately after collection, and staff kept the samples cool during packaging and transport to prevent specimen degradation. All urine and serum samples were transferred to polypropylene microcentrifuge tubes and stored in freezers at -80 °C (serum) and -20 °C (urine), respectively. The series of collection process and collection purpose were approved by National Taiwan University Hospital (NTUH) Institutional Review Board (IRB) and the verified number is 201803109RINB.

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2.3 Sample preparation

Samples were thawed in a 4°C refrigerator for at least 3 hours prior to analysis. Each sample was spiked with 50 μL 200 ng/mL of isotope-labeled internal standards (ISTDs) in methanol to correct for matrix effects and systematic errors for more accurate quantification. The concentration level of the 11 ISTDs when spiked is 100 ng/mL. The 11 ISTDs are MnBP-$^{13}C_4$, MnOP-D_4, oxo-MPHP-$^{13}C_4$, MHINP-D_4, MCINP-D_4, MEHP-$^{13}C_4$, MECPP-$^{13}C_4$, OH-MINCH-D_8, MEP-$^{13}C_4$, MBzP-$^{13}C_4$ and MECPTP-D_4 respectively.

Initially, the volume of each urine sample was 1 mL in a polypropylene microcentrifuge tube and 150 μL urine was drawn into a 1.5 mL eppendorf tube for analysis. We spiked 150 μL 10mM ammonium acetate$_{(aq)}$ and 50 μL 500 ng/mL 4-methylumbelliferyl sulfate (4-MUS) and 4-methylumbelliferyl-β-D-glucuronide (4-MUG) mixture in methanol. The use of ammonium acetate is in order to establish a stable pH for enzymatic hydrolysis, and a mixture of 4-MUS and 4-MUG is to confirm whether the enzyme works properly. Next, 45 μL of β-glucuronidase and arylsulfatase (ALS) mixed enzymes were added to the urine samples and incubated at 37°C for 40 minutes in order to deconjugate. After the deconjugation process, 50 μL 200 ng/mL of ISTDs was spiked and 405 μL of acetonitrile was added to precipitate proteins. The mixture was vortexed for 5 seconds and transferred to a Sirocco 96-well protein precipitation plate. Then we used vacuum pump for filtration

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step, and the pressure of the system was -15 kPa to -60 kPa. The remaining solution was collected then 20 μL of dimethyl sulfoxide (DMSO) was added, after that the concentration process proceeded with a Savant SPD1010 SpeedVac at 50 °C for 2 hours 30 minutes. The concentrate was approximately 20 μL and was reconstituted with 80 μL of methanol and vortexed for 15 seconds. After that, the solution was transferred to 150 μL inserts and centrifuged at 3000 rpm for 15 minutes in a Compact Tabletop Centrifuge. The supernatant was then transferred to another insert, subjected to a second centrifugation process, and finally the urine sample was ready for analysis.

2.4 Instrumental analysis

The MS instrument we used was Waters Xevo TQ-XS tandem mass spectrometer (Waters, Milford, USA) (Figure 2). The liquid chromatography system was Waters ACQUITY UPLC I-Class Plus system (Waters, Milford, USA), and the ion source were Waters UniSpray ionization source (IonSense, MA, USA). All the phthalates were detected under negative-ion mode. There are 12 different phthalates as our targeted compounds.

In MS conditions, data were acquired under multiple reaction mode (MRM). We used UniSpray negative mode for analysis. The parameters for MS were 2.5 kV for impactor voltage, 450 ˚C for desolvation temperature, 900 L/hr for desolvation gas flow, 150 L/hr

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for cone gas flow, 7.0 Bar for nebulizer pressure, 0.16 mL/min for collision gas flow, and 120 ˚C for source temperature (Table 2).

And in UPLC conditions, we used Atlantis Premier BEH C18 AX (50 x 2.1 mm, 1.7 μm; Waters) to separate 12 different phthalates. The column temperature was 30 ˚C . The mobile phase consists of (A) 5 mM ammonium acetate$_{(aq)}$ and (B) MeOH + 5 mM ammonium acetate$_{(aq)}$. The gradient began from 70% A and 30% B for 0.5 minutes, and then the organic phase increased to 100% at 7.5 minutes and held for 0.5 minutes. Next, the organic phase decreased sharply within 0.2 minutes back to 30%, and held for 1.8 minutes for column re-equilibrium, in total of 10 minutes (Table 3).

2.5 Quality assurance and quality control

A batch of 48 samples was processed each time. Each batch contained 6 quality control samples, including a reagent blank (Milli-Q water with 50 μL 200 ng/mL ISTDs), a matrix blank (with 50 μL 200 ng/mL ISTDs), two matrix spiked samples (with 25 μL 400 ng/mL ISTDs and 25μL 300 ng/mL standards), a pre-spiked real sample (QC spike with 25 μL 400 ng/mL ISTDs and 25μL 300 ng/mL standards) and a duplicate real sample (QC duplicate with 50 μL 200 ng/mL ISTDs). The blank matrixes were Medidrug Baseline U. We inspected the relative percent difference (RPD%) of duplicate real samples and two pre-spiked matrix samples, and examined the biases of pre-spiked samples for quality control. The identity confirmation of chemicals followed the guidance of 2002/657/EC

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and SANTE/SANCO criteria from the European Commission (41; 42).

The efficiency of deconjugation enzyme were tested by adding 500 ng/mL 4-MUG and 4-MUS into each sample. The signal intensity of 4-MUG and 4-MUS were fewer than that of 50 ng/mL 4-MUS and 4-MUG and appearing signal intensity of 4-MU higher than that of 50 ng/mL 4-MU indicated that the efficiency of deconjugation process were well.

A Waters isolator column (BEH C18, 50 x 2.1 mm, 2.6 μm) was installed in front of the UPLC mixing chamber to reduce background noise in the mobile phase solution. All reusable glassware was washed three times with methanol and acetone after use and covered with aluminum foil before drying in a chemical fume hood.

2.6 Statistical analysis

The significance level was set at $p < 0.05$, and all statistical analyses were operated by SAS version 9.4 and R version 4.1.1 programming language. The statistical analysis and data presentation were for raw unweighted data and creatinine-adjusted concentrations for the statistical analysis of urine samples. Geometric mean (GM), 95% Cis, detection rate, minimum, selected percentiles (25th, 50th, 75th, and 95th) and maximum of phthalate metabolite levels were calculated. Data below limit of detection (LOD) levels were calculated as square root 2 of the detection limit of each phthalate metabolite. Chi-squared, Mann–Whitney U, and Kruskal–Wallis tests were used to evaluate differences in demographic data and levels of phthalate metabolites among sex, age, region, and

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education levels groups. We also use extrapolation to calculate the total population of different ages in Taiwan. The 2019 demographic data of the total population of each age group was provided by the Department of Household Registration in Taiwan.

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Chapter 3. Results

3.1 Characteristics of study participants

From the HBM survey, we selected 1,575 participants for participation in this study (excluded 170 participants without urine collection and 3 participants without urine creatinine data). Demographic information was shown in Table 4. The gender distribution was nearly identical across the population. The majority of participants were over the age of 18 (n = 1312, 83.3%). The total population was divided into 4 different age groups as 7-12 years old, 13-18 years old, 19-64 years old and ≥ 65 years old based on their physiological differences. As for lifestyle habits, 14 times a month and 21 times a month was selected as the frequency cutoff for the eating out questionnaire because of phthalate metabolism (urinary excretion within 48 hours). For other questions, such as smoking and passive smoking, we divided them into two groups based on yes or no questions. In addition, in the environmental survey regarding the age of houses, we divided the respondents into four groups over a period of 10 years. We also defined five different regional groups: Northern (New Taipei, Taipei, Keelung and Yilan), Southern and Remote (Chiayi, Tainan and Penghu), Eastern (Taoyuan, Hsinchu and Miaoli), Western and Southern (Hualien, Taitung, Kaohsiung and Pingtung) and Central (Nantou, Changhua, Yunlin and Taichung). We found that age older than 18 years old group had more frequent behaviors than the 7 to 18 years old group, such as smoking habits and medication usage

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with statistical significance. On the other hand, 7-12 years old group have higher eating out frequency (35.3% > 21 times/per month) when compare to other age groups (30.9%, 22.7%, 10.5%).

3.2 Urinary phthalate metabolite levels in different age groups

The levels of creatinine-adjusted 12 different phthalate metabolites are presented in Table 5. Participants were categorized as 7–12 years old (n = 136), 13–18 years old (n = 127), 19–64 years old (n = 622), and ≥65 years old (n = 690), and urinary phthalate metabolites were analyzed about their selected percentiles and geometric mean (GM) (95% CI) of entity level. MEHP, MECPP, MiBP, MnBP, MHINP, oxo-MPHP and MECPTP had >70% detection rates, while MBzP, MEP, MnOP, MCINP and OH-MINCH had <70% detection rates. Most groups such as MEHP, MECPP, MnBP, MiBP, MHINP, MCINP, oxo-MPHP, OH-MINCH and MECPTP had significantly higher concentrations levels in the 7–12 years old group and ≥65 years old group than in other age groups; nevertheless, on the contrary, the concentration of MEP in the 7-12 years old group was lower than in the other age groups significantly. And the lowest geometric mean of MBzP (GM: 0.34 μg/g cr.) and MnOP (GM: 0.08 μg/g cr.) were found in the 13-18 years old group.

3.3 Urinary phthalate metabolite levels in different region group

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The median levels of creatinine-adjusted 12 different phthalate metabolites separated by 4 different regions groups are presented in Table 6. We defined our 20 cities or counties into four different regional groups: Northern (New Taipei, Taipei, Keelung, Taoyuan, Hsinchu and Yilan), Southern and Remote (Chiayi, Tainan, Kaohsiung, Pingtung and Penghu), Eastern (Hualien and Taitung), Western and Central (Nantou, Changhua, Yunlin, Taichung and Miaoli) by definition made by National Development Council in Taiwan 2022. Phthalate metabolites concentration median about MEP and MECPP had significantly higher concentrations levels in the southern group (6.30 μg/g cr., 8.30 μg/g cr.) than in other region groups. And the concentration median of MiBP (3.33 μg/g cr.), MBzP (0.58 μg/g cr.) and MECPTP (1.93 μg/g cr.) were highest in northern region group. In addition, in eastern region group, we found the concentration median of oxo-MPHP (0.90 μg/g cr.) was significantly higher than in others region group. And the concentration difference about MnBP, MEHP, MnOP, MHINP, MCINP and OH-MINCH were not statistically significant.

3.4 RVs for urinary phthalate metabolites

We set up our 95 percentiles data as RVs for urinary phthalate metabolites in different age groups in Taiwan (Table 7). In 7–12 years old group RVs of urinary MEHP (18.9 μg/L), MECPP (81.1 μg/L), MiBP (47.1 μg/L), MnBP (72.9 μg/L), MBzP (1.9μg/L),

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MnOP (0.9 μg/L), MHINP (26.3 μg/L), MCINP (2.2 μg/L) oxo-MPHP (4.7 μg/L) and OH-MINCH (7.2 μg/L) were the highest RVs in all age groups. In contrast, the highest RVs of urinary MEP (95.8 μg/L) and MECPTP (32.4 μg/L) were in ≥ 65 years old group and 19-64 years old group respectively. Comparison with other national surveys can find that RVs of phthalates metabolites, especially to DBP and DEHP metabolites, were higher in Taiwan than in other countries (Table 7 & 8). On the other hand, the RVs of MEP and MBzP in other countries and the substitutes of plasticizers DINCH and DEHTP metabolites in the NHANES studies were higher than those of our Taiwan HBM study.

3.5 Exceedances of HBM I values or HBM-GVs in Taiwan HBM for each phthalate metabolite

To assess the health relevance of phthalate exposure, urinary metabolite levels were compared with corresponding HBM-I values and HBM-GVs in children and adults. Such as Σ of OH-MINCH + Cyclohexane-1,2-dicarboxylate-mono-7-carboxylate-4-methyl heptyl ester (cx-MINCH) based on nephrotoxic effects, and Σ of OH-MPHP + oxo-MPHP based on thyroid and pituitary gland effects.

For MBzP and MECPTP, none of samples in Taiwan HBM exceeded the HBM-I values or HBM-GVs of 2.00 mg/L, 3.00 mg/L for MBzP and 1.80 mg/L, 2.80 mg/L for MECPTP (Table 10). For MnBP, 0.42% of the participating children, all in the age group of 7–13

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years old, exceeded the HBM-GVs value of 0.12 mg/L urine. Extrapolated to the reference population in Taiwan, would represent ~5892 children. As well as 0.13% of participating adolescents and adults, all in the age group of ≥ 14 years old, exceeded the HBM-GVs value of 0.19 mg/L urine. Extrapolated to the reference population in Taiwan, would represent ~27582 persons. And for MiBP, 0.83% of the participating children, all in the age group of 7-13 years, exceeded the HBM-GVs of 0.16 mg/L urine. Extrapolated to the reference population in Taiwan, this would represent ~11784 children. As well as 0.07% of participating adolescents and adults, all in the age group of ≥ 14 years old, exceeded the HBM-GVs value of 0.23 mg/L urine. Extrapolated to the reference population in Taiwan, would represent ~13791 persons. And for oxo-MPHP, 0.20% of participating adolescents and adults, all in the age group of ≥ 14 years old, exceeded the HBM-GVs value of 0.29 mg/L urine. Extrapolated to the reference population in Taiwan, would represent ~41373 persons. By contrast, none of the participating children exceeded the HBM-GVs of urine for oxo-MPHP. Due to the HBM-I and HBM-GVs values of DEHP and DINCH metabolites are combined metabolite types (MECPP + Mono 2-ethyl-5-hydroxyhexyl phthalate (5-OHMEHP), OH-MINCH + cx-MINCH). And the DEHP metabolite 5-OHMEHP as well as the DINCH metabolite cx-MINCH were not analyzed in this study. Therefore, it was not possible to calculate excess DEHP and DINCH by using HBM-I and HBM-GVs values in our Taiwan HBM study.

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Chapter 4. Discussion

This is the first study to assess nationwide representative exposure to phthalate metabolites in the general population of Taiwan. Although, we observed that some phthalate metabolites are significantly higher in some region group than in the others. Nevertheless, because of seasonal and regional effects, our data must be collected four consecutive years to be available for regionally representative; therefore, a high value in one region cannot be represent the exposure in that area directly in this study. However, our study still has year representative in 2019 in Taiwan for general population.

In difference of age groups, concentrations of most phthalate metabolites in urine were higher in the 7 to 12 years old group than in the ≥13 years old group. When compared directly to adolescents and adults, children have higher levels of phthalate metabolites, which has also been shown in other studies. Results from a previous study showed the same result of significantly higher DEHP exposure in Taiwanese boys aged 7 to 17 years than in girls and adults (47). And factors in this situation might be the frequency of mouth habits, dust intake from playing near the ground, or higher food intake relative to the child's weight (45, 46). Compared to adults, children's exposure to phthalates has a relatively low threshold, so more attention should be paid to in this age group, and the government should keep follow up on children's exposure to phthalates continuously.

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By contrast in MEP concentration, MEP is significantly higher in old age groups in Taiwan than in children and adolescent groups. Previous study indicated that urinary MEP levels were most strongly positively associated with personal care products, especially perfume use (20, 59, 60). Due to DEP are used extensively in personal care products, cosmetics and cigarettes, children, usually without the habit of using cosmetics and smoking, will have relatively low exposure when compare to adults.

When compared with previous studies in Taiwan, phthalate metabolites median levels in pregnant women and children were lower than before (Table 11). After 2011 phthalates scandal happened, we observed that urinary phthalate metabolites such as MEHP, MnBP, MiBP, MBzP and MEP were declined year by year in Taiwan in other studies. Levels of phthalate metabolites in the general population declining in recent years in Taiwan showed that people were becoming more aware of environmental contaminants in food. And a series of control policies were implemented by government was managing this food safety issue well (2, 63, 64). And in this Taiwan HBM study, most of phthalate metabolites concentration levels were significantly lower than past researches in Taiwan; however, when we make a comparison with other national surveys (Table 7 & 8), we can find that exposure to phthalates, especially to DBP and DEHP metabolites, was still higher in Taiwan than in other countries. Therefore, intervention strategies in order to reduce exposure to phthalates is still need further investigation.

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On the other hand, urinary BBzP metabolites are significantly lower in the general population in Taiwan than in European and American countries. The metabolite MBzP was detected at a low detection rate of 10% to 30% in urine samples from Asian countries, but detected in almost all samples from most European countries in other studies. Relatively high levels of DEHP were detected in Taiwan, but low levels of BBzP were detected compared to the global average. As BBzP is mainly used in PVC-based flooring, and is used less in Taiwanese home decoration than in previous years. Urinary MBzP levels were lower than those of MBP, MiBP, or MEP worldwide, and MBzP was detected in previous studies in almost all urine samples from the European region, but not in Asian countries either (26, 61, 62). Since MBzP is the major metabolite of BBzP, the low detection of MBzP indicated the low exposure to BBzP in the general Taiwanese population.

Furthermore, we can see that OH-MINCH, oxo-MPHP, and MECPTP, which are phthalate substitutes metabolites, were lower than other national surveys. As this is the first nationwide representative study to analyze urinary metabolites levels of phthalate substitutes in Taiwan, there were no previous data for comparison. However, recent studies such as NHANES over the past 6 years showed that the metabolites of DINCH, DPHP and DEHTP were increasing year by year (Table 9). Although the levels of phthalate substitutes in Taiwan were lower than other countries at 2019, the alternative

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use of phthalate substitutes appears to be the future that will be realized in one day. Theirs not explicitly health effects and associated political controls need continued monitoring and improvement.

As we knew that each country's plastics industries differ in terms of process usage habits. Country-specific data might not be directly available to compare country-to-country differences. However, RVs from these nationally representative surveys can still be used and compared to HBM-I values and HBM-GVs in order to understand the exposure of the general population in different countries. And it can also be used as a recommended standard for national policies.

This study had some limitations regarding the interpretation of the data. This was a cross-sectional study. Data reflected participant exposures immediately prior to study only. However, only if given constant and ubiquitous exposure to phthalates that their metabolites levels might provide modest predictive value for exposure of people. Moreover, this study did not consider behavioral characteristics or sociodemographic that may have influenced phthalate exposure in general population in the first beginning. Therefore, we did not use questionnaire data with phthalate metabolites concentrations level for exposure assessment. Despite the limitations of the current study, it still included a large number of samples and investigated different regions of nearly whole Taiwan in

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2019. Subject to sufficient participation, we will provide phthalate metabolite values and RVs to Taiwan for use in future public health applications.

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Chapter 5. Conclusions

Chemical safety and substitution regulations and advices can help reduce the overall chemical hazards that phthalates pose to the environment and human health. This is the first study to systematically assess nationwide exposure to phthalates in the general population of Taiwan. Most phthalates metabolites were higher in the 7-12 years old group than in other age groups. Also, we observed that the levels of phthalates metabolites, especially the DBP and DEHP metabolites, were decreased with increasing age. And the RVs of DEHP and DBP metabolites were still higher than other countries studies. When urinary phthalate metabolite levels were compared with corresponding HBM-I values and HBM-GVs in children and adults. We still found that there are still some people who have exceeded the standard with health-related concerns.

The RVs employment is very important in knowing the levels that public is now exposed to these chemical hazards. With HBM survey, which is nationally representative of its kind, allows us to monitor phthalates exposure in Taiwan and make recommendations to the government in order to improve our living conditions. Hoping that our findings can contribute to promoting Taiwan's phthalates regulation aimed at protecting Taiwanese people from the risk of phthalates exposure. We will continue to monitor the general population of Taiwan annually through the nationwide HBM survey.

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Figures

Figure 1. Decision tree for determining HBM-GVs (taken from Apel et al., 2023).

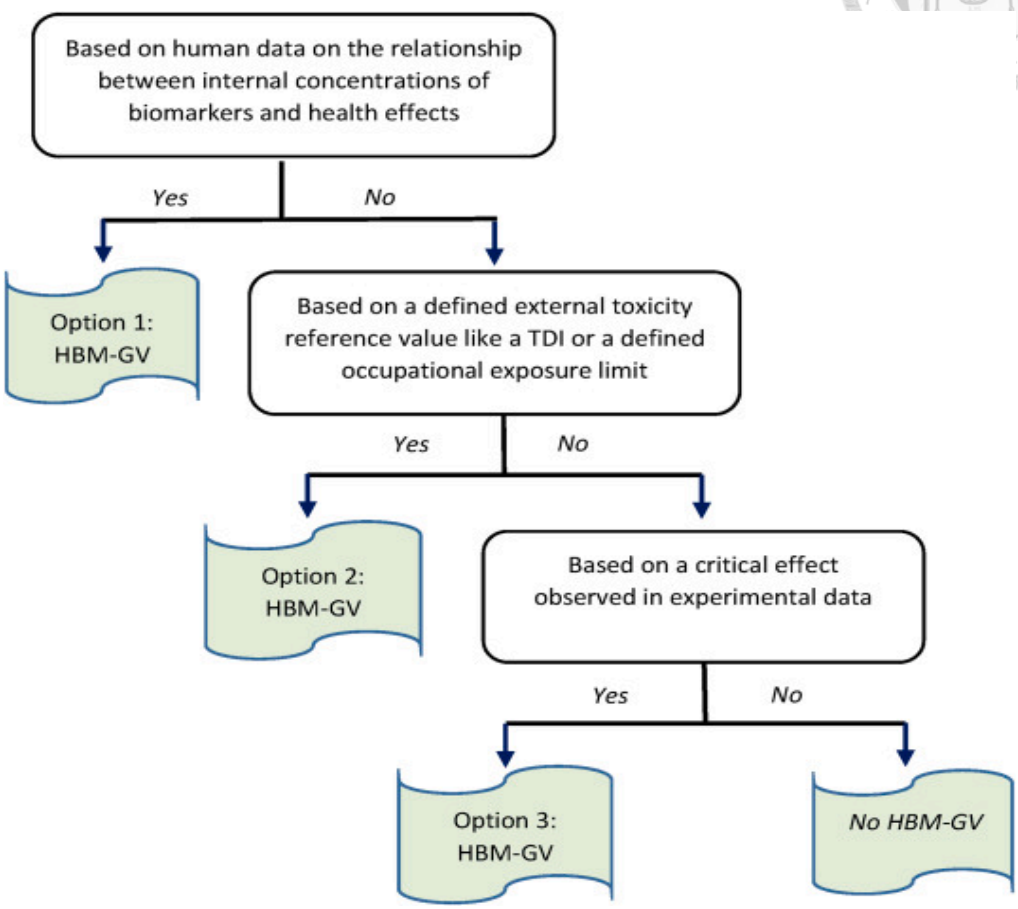

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Figure 2. UPLC I-Class /Xevo TQ-XS tandem mass spectrometer.

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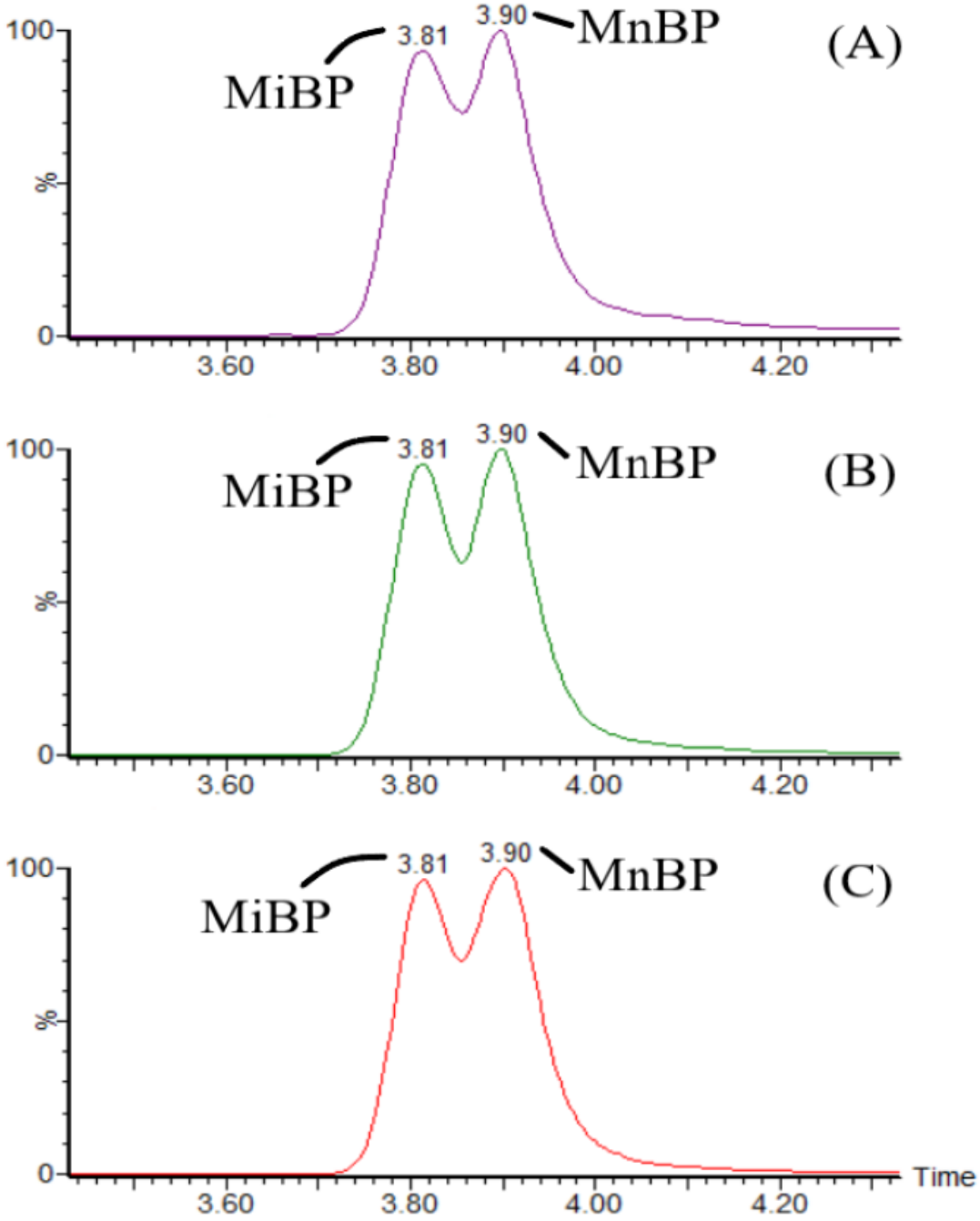
Figure 3. Chromatograms of MnBP and MiBP in different concentrations.



(A) chromatograms of 10 ng/mL MnBP and MiBP in methanol

(B) chromatograms of 50 ng/mL MnBP and MiBP in methanol

(C) chromatograms of 100 ng/mL MnBP and MiBP in methanol

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Tables

Table 1. Human biomonitoring guidance values for the general population (HBM-GV_{GenPop}) or HBM-I value derived for selected phthalates and substitutes.

Parent compound	Metabolites	HBM-GV_{GenPop} or HBM-I value in μg/L	
		Children [a]	Adolescents and adults [b]
DEHP	5-oxo-MEHP + 5-OHMEHP	340 [c]	500
	MECPP + 5-OHMEHP	380	570
DnBP	MnBP	120	190
DiBP	MiBP	160	230
BBzP	MBzP	2000	3000
DPHP	oxo-MPHP	190	290
	OH-MPHP	140	220
DINCH	OH-MINCH + cx-MINCH	3000	4500
DEHTP	MECPTP	1800 [d]	2800

DEHP: di (2-ethylhexyl) phthalate;5-oxo-MEHP: Mono(2-ethyl-5-oxohexyl) phthalate; 5-OHMEHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; DnBP: Di-n-butyl phthalate; MnBP: Mono-n-butyl phthalate; DiBP: di-iso-butyl phthalate; MiBP: Mono-iso-butyl phthalate; BBzP: butyl benzyl phthalate; MBzP: Mono-benzyl phthalate; DPHP: di-(2-propylheptyl) phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; DINCH: di-iso-nonyl-cyclohexane-1,2-dicarboxylate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; cx-MINCH: Cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl) heptyl ester; DEHTP: di-2-ethylhexyl terephthalate; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. Including children 6–13 years of age.
b. Including women of child-bearing age.
c. HBM-GVs data taken from Lange et al., 2021.
d. HBM-I value for MECPTP data taken from Apel et al., 2017.

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Table 2. MS conditions about parameters setting.

MS parameters	Values
Impactor voltage (kV)	2.5
Desolvation temperature (˚C)	450
Desolvation gas flow (L/hr)	900
Cone gas flow (L/hr)	150
Nebulizer (Bar)	7.0
Collision gas flow (mL/min)	0.16
Source temperature (˚C)	120

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Table 3. UPLC conditions of gradient and others setting.

Column	Atlantis Premier BEH C18 AX (50 x 2.1 mm, 1.7 μm)		
Temperature	30°C		
Flow rate	0.5 mL/min		
Injection volume	2 μL		
Mobile phase	A：5 mM ammonium acetate $_{(aq)}$ B：MeOH + 5 mM ammonium acetate $_{(aq)}$		
Gradient		A	B
	Initial	70	30
	0.5	70	30
	7.5	0	100
	8.0	0	100
	8.2	70	30
	10.0	70	30

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Table 4. Demographic characteristics of participants in Taiwan HBM 2019 study (N = 1575).

Characteristics	Items	All participants (N = 1575)	7-12 years old (N = 136)	13-18 years old (N = 127)	19-64 years old (N = 622)	≥65 years old (N = 690)	*p*-values [a]
		N (%)	N (%)	N (%)	N (%)	N (%)	
Sex	Male	799 (50.7%)	74 (54.4%)	61 (48.0%)	310 (49.8%)	354 (51.3%)	0.71
	Female	776 (49.3%)	62 (45.6%)	66 (52.0%)	312 (50.2%)	336 (48.7%)	
Region [b]	Northern	338 (21.5%)	26 (19.1%)	20 (15.8%)	140 (22.5%)	152 (22.0%)	0.25
	Southern & Remote	298 (18.9%)	33 (24.3%)	29 (22.8%)	113 (18.1%)	123 (17.9%)	
	Eastern	282 (17.8%)	25 (18.4%)	18 (14.2%)	114 (18.3%)	125 (18.1%)	
	Western	328 (20.9%)	25 (18.4%)	22 (17.3%)	136 (22.0%)	145 (21.0%)	
	Central	329 (20.9%)	27 (19.8%)	38 (29.9%)	119 (19.1%)	145 (21.0%)	
House age [c]	1 to 10 years	194 (12.5%)	17 (12.7%)	38 (30.9%)	88 (14.4%)	51 (7.5%)	<0.001***
	10 to 20 years	393 (25.3%)	45 (33.6%)	23 (18.7%)	186 (30.4%)	139 (20.4%)	
	20 to 30 years	484 (31.1%)	45 (33.6%)	35 (28.5%)	178 (28.8%)	226 (33.1%)	
	> 30 years	485 (31.1%)	27 (20.2%)	27 (22.0%)	164 (26.5%)	267 (39.1%)	
Education level [d]	below high school	1203 (76.9%)	94 (70.7%)	100 (81.3%)	388 (62.6%)	621 (90.3%)	<0.001***
	above Bachelor degree	361 (23.1%)	39 (29.3%)	23 (18.7%)	232 (37.4%)	67 (9.7%)	

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Characteristics	Items	All participants (N = 1575)	7-12 years old (N = 136)	13-18 years old (N = 127)	19-64 years old (N = 622)	≥65 years old (N = 690)	*p*-values [a]
		N (%)	N (%)	N (%)	N (%)	N (%)	
Income (per month) [e]	< 40 thousand	1071 (70.4%)	21 (17.4%)	23 (20.4%)	442 (72.3%)	585 (86.8%)	<0.001***
	40 to 60 thousand	227 (15.0%)	26 (21.5%)	24 (21.2%)	114 (18.7%)	63 (9.3%)	
	> 60 thousand	222 (14.6%)	74 (61.1%)	66 (58.4%)	56 (9.0%)	26 (3.9%)	
Medication use [f]	Yes	697 (46.3%)	11 (8.3%)	2 (3.1%)	195 (31.4%)	489 (71.1%)	<0.001***
	No	808 (53.7%)	122 (91.7%)	62 (96.9%)	425 (68.6%)	199 (28.9%)	
Smoking [g]	Yes	171 (12.0%)	0 (0.0%)	1 (0.8%)	103 (17.9%)	67 (10.3%)	<0.001***
	No	1252 (88.0%)	75 (100.0%)	120 (99.2%)	473 (82.1%)	584 (89.7%)	
Passive smoking [h]	Yes	967 (64.2%)	48 (64.0%)	94 (74.6%)	440 (70.9%)	385 (56.2%)	<0.001***
	No	540 (35.8%)	27 (36.0%)	32 (25.4%)	181 (29.1%)	300 (43.8%)	
Eat out rate (per month) [i]	< 14 times	908 (57.9%)	44 (33.1%)	36 (28.6%)	306 (49.3%)	522 (75.9%)	<0.001***
	14 to 21 times	361 (23.0%)	42 (31.6%)	51 (40.5%)	174 (28.0%)	94 (13.7%)	
	> 21 times	299 (19.1%)	47 (35.3%)	39 (30.9%)	141 (22.7%)	72 (10.5%)	

a. Chi-square test was applied. *p < 0.05, **p < 0.01, ***p < 0.001.

b. Northern group included Taipei City, New Taipei City, Keelung City and Yilan County; Southern & Remote group included Tainan City, Penghu County, Chiayi City and Chiayi County; Eastern group included Hualien County, Taitung County, Pingtung County and Kaohsiung

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City; Western group included Taoyuan City, Miaoli County, Hsinchu City and Hsinchu County; Central group included Taichung City, Changhua County, Yunlin County and Nantou County.

c. 2, 4, 6 and 7 missing data in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

d. below 18 years old group use primary caregiver's education level. 3, 4, 2 and 2 missing data in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

e. below 18 years old group use family income. 15, 14, 10 and 16 missing data of family income in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

f. 3, 63, 2 and 2 missing data of medication use in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

g. 61, 6, 46 and 39 missing data in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

h. 61, 1, 1 and 5 missing data in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

i. 3, 1, 1 and 2 missing data in 7-12, 13-18, 19-64 and ≥65 years group, respectively.

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Table 5. Geometric mean, minimum, maximum, and selected percentiles of urine creatinine (mg/dL) and phthalate metabolites levels (μg/g creatinine) in Taiwan HBM 2019 study.

	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
Creatinine (mg/dL)										
7-12 yrs	136		100.43 (91.65-110.05)	13.00	68.30	102.90	155.30	231.80	349.70	
13-18 yrs	127		136.02 (124.26-148.89)	41.00	94.20	145.70	196.70	284.40	462.50	<0.001***
19-64 yrs	622		84.02 (80.07-88.16)	14.80	54.40	84.40	130.20	225.20	343.50	
≥ 65 yrs	690		58.36 (55.90-60.93)	11.80	39.30	57.65	87.90	151.70	289.10	
Phthalates (μg/g creatinine)										
MEP										
7-12 yrs	136	71.32%	6.38 (5.23-7.78)	0.79	2.91	5.63	12.81	50.87	252.37	
13-18 yrs	127	81.10%	5.50 (4.49-6.74)	0.60	2.38	4.44	13.27	36.08	117.08	0.02*
19-64 yrs	622	64.31%	6.82 (6.10-7.62)	0.40	2.37	5.11	15.04	83.52	1871.88	
≥ 65 yrs	690	56.09%	8.14 (7.32-9.05)	0.72	3.13	5.74	14.30	152.14	7298.86	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MnBP										
7-12 yrs	136	100%	13.16 (11.35-15.25)	0.48	7.20	12.62	24.60	48.43	177.99	
13-18 yrs	127	100%	8.03 (7.03-9.16)	1.47	4.66	7.82	13.46	24.88	83.90	
19-64 yrs	622	99.84%	6.22 (5.78-6.70)	0.03	3.17	5.78	10.15	33.18	238.17	<0.001***
≥ 65 yrs	690	100%	7.56 (7.03-8.13)	0.48	3.81	6.70	13.03	46.43	270.28	
MiBP										
7-12 yrs	136	100%	6.28 (5.37-7.34)	0.73	3.50	5.79	10.47	30.89	149.63	
13-18 yrs	127	100%	3.68 (3.18-4.25)	0.76	2.09	3.37	6.58	14.07	65.17	
19-64 yrs	622	100%	2.88 (2.70-3.08)	0.28	1.67	2.70	4.76	11.41	1187.18	<0.001***
≥ 65 yrs	690	100%	3.14 (2.96-3.33)	0.51	1.83	2.94	4.97	12.46	125.11	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MEHP										
7-12 yrs	136	100%	3.76 (3.27-4.32)	0.48	2.19	3.59	6.86	13.99	22.28	
13-18 yrs	127	100%	2.26 (2.00-2.56)	0.47	1.25	2.27	4.01	6.61	11.15	
19-64 yrs	622	99.84%	2.42 (2.27-2.58)	0.13	1.42	2.47	4.13	9.07	38.60	<0.001***
≥ 65 yrs	690	100%	2.96 (2.78-3.14)	0.14	1.72	2.94	5.06	11.30	33.45	
MECPP										
7-12 yrs	136	100%	15.78 (13.92-17.89)	2.32	9.25	15.54	24.09	67.82	99.63	
13-18 yrs	127	100%	8.39 (7.38-9.53)	2.02	5.06	7.95	12.90	33.81	60.44	
19-64 yrs	622	98.71%	6.55 (6.16-6.97)	0.44	4.20	6.36	10.44	23.30	788.55	<0.001***
≥ 65 yrs	690	98.84%	8.57 (8.12-9.05)	1.11	5.41	8.31	13.04	29.25	168.79	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MBzP										
7-12 yrs	136	28.67%	0.46 (0.40-0.53)	0.10	0.28	0.42	0.67	1.56	13.75	
13-18 yrs	127	27.56%	0.34 (0.29-0.39)	0.10	0.21	0.29	0.50	1.04	21.41	
19-64 yrs	622	12.06%	0.46 (0.44-0.49)	0.10	0.30	0.45	0.70	1.30	11.91	<0.001***
≥ 65 yrs	690	12.46%	0.66 (0.63-0.70)	0.14	0.43	0.64	0.98	1.97	15.35	
MnOP										
7-12 yrs	136	70.59%	0.15 (0.13-0.18)	0.02	0.08	0.13	0.22	1.08	11.50	
13-18 yrs	127	63.78%	0.08 (0.07-0.10)	0.02	0.05	0.08	0.15	0.30	0.80	
19-64 yrs	622	44.86%	0.16 (0.15-0.18)	0.02	0.08	0.15	0.30	0.92	5.48	<0.001***
≥ 65 yrs	690	37.97%	0.21 (0.20-0.23)	0.02	0.11	0.19	0.35	1.25	5.45	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MHINP										
7-12 yrs	136	99.26%	4.27 (3.66-4.97)	0.38	2.44	3.80	6.36	20.71	304.89	
13-18 yrs	127	94.49%	2.82 (2.31-3.44)	0.15	1.47	2.60	4.96	27.12	102.19	
										<0.001***
19-64 yrs	622	66.08%	1.19 (1.10-1.28)	0.16	0.67	1.04	1.80	6.21	145.83	
≥ 65 yrs	690	57.54%	1.37 (1.28-1.46)	0.17	0.78	1.21	2.06	7.38	218.65	
MCINP										
7-12 yrs	136	86.03%	0.39 (0.34-0.45)	0.07	0.24	0.36	0.59	1.58	11.84	
13-18 yrs	127	80.31%	0.23 (0.20-0.27)	0.03	0.13	0.21	0.40	1.07	3.53	
										<0.001***
19-64 yrs	622	40.51%	0.16 (0.15-0.17)	0.03	0.10	0.15	0.23	0.53	88.11	
≥ 65 yrs	690	31.88%	0.21 (0.20-0.22)	0.04	0.13	0.20	0.31	0.71	2.87	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
oxo-MPHP										
7-12 yrs	136	100%	1.01 (0.90-1.15)	0.24	0.60	0.93	1.65	6.30	7.30	
13-18 yrs	127	100%	0.73 (0.63-0.86)	0.09	0.41	0.65	1.09	3.04	161.73	
										<0.001***
19-64 yrs	622	100%	0.58 (0.53-0.62)	0.05	0.31	0.55	0.96	2.45	3123.26	
≥ 65 yrs	690	100%	0.75 (0.70-0.80)	0.11	0.41	0.66	1.20	3.53	86.08	
OH-MINCH										
7-12 yrs	136	71.32%	0.78 (0.64-0.95)	0.08	0.32	0.66	1.67	7.27	32.31	
13-18 yrs	127	64.57%	0.45 (0.38-0.55)	0.09	0.22	0.35	0.87	3.24	12.73	
										<0.001***
19-64 yrs	622	32.96%	0.46 (0.42-0.51)	0.04	0.23	0.39	0.68	4.88	144.40	
≥ 65 yrs	690	31.16%	0.66 (0.61-0.71)	0.10	0.33	0.54	1.01	5.56	156.90	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MECPTP										
7-12 yrs	136	100%	3.02 (2.53-3.59)	0.34	1.68	2.84	4.49	18.70	372.53	
13-18 yrs	127	100%	1.98 (1.58-2.49)	0.14	0.87	1.62	3.44	20.00	242.10	
19-64 yrs	622	95.66%	1.75 (1.55-1.98)	0.05	0.65	1.36	3.90	31.30	1076.51	<0.001***
≥ 65 yrs	690	93.19%	1.87 (1.67-2.08)	0.08	0.68	1.63	4.37	29.01	3476.45	

HBM: Human biological monitoring; LOD: Low of detection; GM: geometric mean; MEP: Mono-ethyl phthalate ; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. LOD data were calculated 1/√2 of detection limit.

b. Comparison of age group by Mann–Whitney U test and Kruskal-Wallis test. *p < 0.05, **p < 0.01, ***p < 0.001.

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Table 6. Comparison of median levels for urinary phthalate metabolites concentration (μg/g creatinine) from different region groups in Taiwan HBM 2019 study.

Region	Northern	Southern	Western	Eastern	
N	577	440	418	140	
	Median	Median	Median	Median	*p*-values [a]
MEP	4.94	6.30	5.45	4.88	0.007**
MiBP	3.33	2.84	3.02	2.62	0.01*
MnBP	6.78	7.04	6.67	6.39	0.46
MEHP	2.79	2.46	2.89	2.73	0.06
MECPP	7.11	8.30	8.22	7.68	< 0.001***
MBzP	0.58	0.47	0.47	0.54	< 0.001***
MnOP	0.16	0.14	0.16	0.15	0.07
MHINP	1.21	1.42	1.32	1.33	0.11
MCINP	0.19	0.18	0.19	0.18	0.80
oxo-MPHP	0.57	0.68	0.64	0.90	< 0.001***
OH-MINCH	0.47	0.42	0.49	0.50	0.14
MECPTP	1.93	1.51	1.33	1.84	0.001**

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HBM: Human biological monitoring; Northern (New Taipei, Taipei, Keelung, Taoyuan, Hsinchu and Yilan), Southern and Remote (Chiayi, Tainan, Kaohsiung, Pingtung and Penghu), Eastern (Hualien and Taitung), Western and Central (Nantou, Changhua, Yunlin, Taichung and Miaoli); MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. Comparison of regions by Mann–Whitney U test and Kruskal-Wallis test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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Table 7. Comparison of 95 percentile levels (μg/L) for urinary phthalate metabolites in 6-19 years old from different countries.

Country	TEST, Taiwan [a]		Taiwan		NHANES, USA [b]		CHMS, Canada [c]		KoNEHS, Korea [d]		GerES V, Germany [e]
Year	2013-2016		2019		2017-2018		2018-2019		2015-2017		2014-2017
Age	7-11	12-17	7-12	13-18	6-11	12-19	6-11	12-19	6-11	12-18	3-17
N	336	257	136	127	306	365	498	504	885	901	2256
	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}
MEHP	63.1	54.3	18.9	8.6	6.8	4.1	4.3	5.5	-	-	6.7
MECPP	221.0	139.8	81.1	46.0	61.2	35.7	34.0	26.0	144.0	89.7	46.1
MiBP	140.8	89.5	47.1	21.7	58.5	37.9	65.0	39.0	-	-	110.0
MnBP	218.3	135.6	72.9	49.2	50.9	50.3	72.0	60.0	126.0	168.0	69.6
MEP	168.7	234.8	58.7	71.2	192.0	322.0	130.0	180.0	-	-	219.0
MBzP	15.6	11.7	1.9	1.4	36.2	33.0	46.0	26.0	24.2	25.3	18.7
MnOP	- [f]	-	0.9	0.5	-	-	< LOD [g]	< LOD [g]	-	-	< LOD [g]
MHINP	-	-	26.3	21.1	-	-	7.5	5.5	-	-	30.2
MCINP	-	-	2.2	1.2	15.4	8.6	3.1	2.2	1.5	1.0	30.2
oxo-MPHP	-	-	4.7	3.7	-	-	-	-	-	-	1.8
OH-MINCH	-	-	7.2	5.3	13.1	10.9	1.4	1.5	-	-	15.8
MECPTP	-	-	23.5	29.7	565.0	693.0	-	-	-	-	48.7

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HBM: Human biological monitoring; MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. Taiwan Environmental Survey for Toxicants 2013–2016 (Liao, 2021).
b. NHANES: National Health and Nutrition Examination survey 2017–2018 (CDC, 2022).
c. CHMS: Canadian Health Measures Survey Cycle 5 2018–2019 (Health Canada, 2022).
d. KoNEHS: Korean National Environmental Health Survey 2015–2017 (Jung, S.K et al., 2022).
e. GerES V: German Environmental Survey 2014–2017 (Schwedler et al., 2020).
f. data not reported.
g. below the limit of detection.

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Table 8. Comparison of 95 percentile levels (μg/L) for urinary phthalate metabolites in ≥ 18 years old from different countries.

Country	TEST, Taiwan [a]	Taiwan		NHANES, USA [b]	CHMS, Canada [c]			KoNEHS, Korea [d]
Year	2013-2016	2019		2017-2018	2018-2019			2015-2017
Age	≥ 18	19-64	≥ 65	≥ 20	20-39	40-59	60-79	≥ 19
N	1264	622	690	1700	324	335	330	3781
	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}	P_{95}
MEHP	59.2	9.7	8.1	4.9	5.8	4.2	3.6	-
MECPP	93.8	22.9	20.0	31.0	21.0	14.0	19.0	131.0
MiBP	70.0	14.1	8.0	33.5	43.0	36.0	39.0	-
MnBP	204.3	35.2	32.0	42.3	49.0	43.0	45.0	125.0
MEP	265.8	86.9	95.8	389.0	180.0	250.0	120.0	-
MBzP	11.7	0.9	1.0	27.2	17.0	13.0	23.0	14.6
MnOP	- [e]	0.9	0.8	-	< LOD [f]	< LOD [f]	< LOD [f]	-
MHINP	-	6.1	4.3	-	8.2	3.7	6.7	-
MCINP	-	0.4	0.4	5.7	2.2	3.9	2.3	1.5
oxo-MPHP	-	2.2	2.1	-	-	-	-	-
OH-MINCH	-	4.1	2.9	8.5	0.94	1.1	0.49	-
MECPTP	-	32.4	16.9	431	-	-	-	-

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HBM: Human biological monitoring; MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. Taiwan Environmental Survey for Toxicants 2013–2016 (Liao, 2021).
b. NHANES: National Health and Nutrition Examination survey 2017–2018 (CDC, 2022).
c. CHMS: Canadian Health Measures Survey Cycle 5 2018–2019 (Health Canada, 2022).
d. KoNEHS: Korean National Environmental Health Survey 2015–2017 (Jung, S.K et al., 2022).
e. data not reported.
f. below the limit of detection.

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Table 9. Internal comparison of 95 percentile levels among different years of NHANES studies for urinary phthalate metabolites with creatinine corrected (μg/g cr.).

Country	**NHANES, USA**								
Year	**2013-2014**			**2015-2016**			**2017-2018**		
Age	**6-11**	**12-19**	**≥20**	**6-11**	**12-19**	**≥20**	**6-11**	**12-19**	**≥20**
N	**409**	**462**	**1814**	**415**	**405**	**1690**	**306**	**365**	**1688**
MEHP	8.3	4.7	5.0	6.2	3.4	5.9	7.0	3.7	4.6
MEHHP	61.7	24.8	22.2	36.6	13.7	20.9	32.8	12.5	17.0
MEOHP	37.4	15.3	13.6	23.9	9.3	13.0	23.3	8.6	11.3
MECPP	97.3	40.7	34.2	62.5	23.2	28.8	57.3	18.6	24.4
MiNP	14.3	11.7	8.9	6.6	3.8	5.0	2.7	3.0	3.5
MiBP	46.4	32.4	23.9	54.3	24.0	27.5	41.4	27.1	25.0
MnBP	56.2	34.1	30.2	58.2	28.0	32.9	47.3	25.7	30.1
MCOCH	- [a]	-	-	5.8	3.6	3.3	8.4	4.0	3.7
OH-MINCH	4.1	1.2	1.4	9.2	6.9	5.4	12.6	6.1	6.2
MECPTP	-	-	-	364.0	395.0	277.0	519.0	479.0	343.0
MEHHTP	-	-	-	63.3	59.5	70.1	79.3	84.9	70.9

NHANES: National Health and Nutrition Examination survey; MEP: Mono-ethyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MEHHP: Mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP: Mono-(2-ethyl-5-oxohexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate;

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MiNP: Mono-isononyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MCOCH: Cyclohexane-1,2-dicarboxylic acid mono carboxyisooctyl ester; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate; MEHHTP: Mono-2-ethyl-5-hydroxyhexyl terephthalate.

a. data not reported.

b. data taken from CDC, 2022.

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Table 10. Exceedances of HBM I values or HBM-GVs in Taiwan HBM 2019 study for DEHP, DBP, BBzP, DPHP, DEHTP and DINCH.

Phthalate metabolites	HBM-I value or HBM-GVs for children [a] (mg/L)	HBM-I value or HBM-GVs for adults [a] (mg/L)	% of Taiwan HBM participants exceeding HBM values in 7-13 years	% of Taiwan HBM participants exceeding HBM values in ≥14 years	Extrapolated for the population in Taiwan aged 7-13 years (N = 1414096) [b]	Extrapolated for the population in Taiwan aged ≥14 years (N = 20797180) [b]
MnBP	0.12	0.19	0.42%	0.13%	~ 5892 persons	~ 27582 persons
MiBP	0.16	0.23	0.83%	0.07%	~ 11784 persons	~ 13791 persons
MBzP	2.00	3.00	0.00%	0.00%	0 person	0 person
oxo-MPHP	0.19	0.29	0.00%	0.20%	0 person	~ 41373 persons
MECPTP	1.80	2.80	0.00%	0.00%	0 person	0 person
MECPP + 5-OHMEHP	0.38	0.57	- [c]	-	-	-
OH-MINCH + cx-MINCH	3.00	4.50	- [d]	-	-	-

HBM: Human biological monitoring; HBM-GVs: Human biological monitoring guidance values; DEHP: di (2-ethylhexyl) phthalate; DnBP: Di-n-butyl phthalate; BBzP: butyl benzyl phthalate; DPHP: di-(2-propylheptyl) phthalate; DEHTP: di-2-ethylhexyl terephthalate; DINCH: di-iso-nonyl-cyclohexane-1,2-dicarboxylate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MBzP: Mono-benzyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate; MECPP: Mono(2-ethyl-5-

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carboxypentyl) phthalate; 5-OHMEHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; cx-MINCH: Cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl) heptyl ester.

a. HBM-I value or HBM-GVs data taken from Apel et al., 2017 and Lange et al., 2021.
b. 2019 demographic data from Dept. of Household Registration in Taiwan.
c. 5-OHMEHP data not analyze in this study.
d. cx-MINCH data not analyze in this study.

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Table 11. Comparison of median levels of urinary phthalate metabolites concentration (μg/g creatinine) in different studies in Taiwan since 2000.

Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
DEHP metabolites				
Lin et al. 2011 in Tainan	2000-2001	Pregnant women	155	MEHP (M: 19.10)
Lin et al. 2011 in Taichung	2001-2002	Pregnant women	99	MEHP (M: 16.37), MECPP (M: 44.69)
		Children at 5 years old	59	MEHP (M: 21.38), MECPP (M: 131.86)
		Children at 2 years old	26	MEHP (M: 21.04), MECPP (M: 206.62)
Huang et al., 2007 in Tainan	2005-2006	Pregnant women	76	MEHP (M: 60.80)
Kuo et al., 2015 in Kaohsiung	2009-2010	Pregnant women	148	MEHP (M: 11.92)
Huang et al., 2017 in Taipei	2010	Pregnant women	112	MEHP (M: 26.27), MECPP (M: 23.13)
Huang et al., 2017 in Taipei, Taichung and Kaohsiung	2012-2013	Children at 3-5 years old	108	MEHP (M: 8.40)
		Children at 6-12 years old	96	MEHP (M: 10.20)
Wu et al., 2018 in northern, central, and southern Taiwan	2012-2013	Children ≤ 12 years old	224	MEHP (M: 10.06)
Tsai et al., 2016 in Taipei, Taichung and Kaohsiung	2012-2013	Children ≤ 18 years old	240	MEHP (M: 36.29)
Wu et al., 2017 in Taiwan	2012-2015	Pregnant women	1631	MEHP (M: 4.91), MECPP (M: 20.56)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
Huang et al., 2020 in Taiwan	2012-2013	Children at 2-14 years old	166	MEHP (M: 9.66)
	2014-2015			MEHP (M: 13.80)
	2016			MEHP (M: 8.22)
36 in Taiwan	2013-2016	7-11 years old	336	MEHP (M: 4.83)
		12-17 years old	257	MEHP (M: 2.12)
		18-39 years old	356	MEHP (M: 4.85)
		40-64 years old	556	MEHP (M: 4.55)
		≥ 65 years old	352	MEHP (M: 12.04)
This study	2019	7-12 years old	136	MEHP (M: 3.59)
		13-18 years old	127	MEHP (M: 2.27)
		19-64 years old	622	MEHP (M: 2.47)
		≥ 65 years old	690	MEHP (M: 2.94)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
DBP metabolites				
Lin et al. 2011 in Taichung	2001-2002	Pregnant women	99	MiBP (M: 15.19), MnBP (M: 87.49)
		Children at 5 years old	59	MiBP (M: 54.13), MnBP (M: 154.53)
		Children at 2 years old	26	MiBP (M: 50.97), MnBP (M: 314.00)
Kuo et al., 2015 in Kaohsiung	2009-2010	Pregnant women	148	MiBP (M: 20.21), MnBP (M: 37.81)
Huang et al., 2017 in Taipei	2010	Pregnant women	112	MiBP (M: 30.17), MnBP (M: 35.28)
Huang et al., 2017 in Taipei, Taichung and Kaohsiung	2012-2013	Children at 3-5 years old	108	MiBP (M: 27.60), MnBP (M: 46.80)
		Children at 6-12 years old	96	MiBP (M: 19.90), MnBP (M: 43.70)
Wu et al., 2018 in northern, central, and southern Taiwan	2012-2013	Children ≤ 12 years old	224	MiBP (M: 24.32), MnBP (M: 46.38)
Tsai et al., 2016 in Taipei, Taichung and Kaohsiung	2012-2013	Children ≤ 18 years old	240	MiBP (M: 92.27), MnBP (M: 172.55)
Wu et al., 2017 in Taiwan	2012-2015	Pregnant women	1631	MiBP (M: 11.28), MnBP (M: 21.50)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
Huang et al., 2020 in Taiwan	2012-2013	Children at 2-14 years old	166	MiBP (M: 26.10), MnBP (M: 46.20)
	2014-2015			MiBP (M: 26.00), MnBP (M: 50.30)
	2016			MiBP (M: 28.80), MnBP (M: 46.30)
36 in Taiwan	2013-2016	7-11 years old	336	MiBP (M: 23.32), MnBP (M: 33.53)
		12-17 years old	257	MiBP (M: 12.85), MnBP (M: 19.51)
		18-39 years old	356	MiBP (M: 8.43), MnBP (M: 15.51)
		40-64 years old	556	MiBP (M: 10.71), MnBP (M: 20.30)
		≥ 65 years old	352	MiBP (M: 12.85), MnBP (M: 18.45)
This study	2019	7-12 years old	136	MiBP (M: 5.79), MnBP (M: 12.62)
		13-18 years old	127	MiBP (M: 3.37), MnBP (M: 7.82)
		19-64 years old	622	MiBP (M: 2.70), MnBP (M: 5.78)
		≥ 65 years old	690	MiBP (M: 2.94), MnBP (M: 6.70)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
DEP metabolites				
Lin et al. 2011 in Tainan	2000-2001	Pregnant women	155	MEP (M: 56.00)
Huang et al., 2007 in Tainan	2005-2006	Pregnant women	76	MEP (M: 68.00)
Kuo et al., 2015 in Kaohsiung	2009-2010	Pregnant women	148	MEP (M: 34.51)
Huang et al., 2017 in Taipei	2010	Pregnant women	112	MEP (M: 36.89)
Wu et al., 2018 in northern, central, and southern Taiwan	2012-2013	Children ≤ 12 years old	224	MEP (M: 13.98)
Tsai et al., 2016 in Taipei, Taichung and Kaohsiung	2012-2013	Children ≤ 18 years old	240	MEP (M: 53.16)
Wu et al., 2017 in Taiwan	2012-2015	Pregnant women	1631	MEP (M: 18.34)
	2012-2013			MEP (M: 13.60)
Huang et al., 2020 in Taiwan	2014-2015	Children at 2-14 years old	166	MEP (M: 11.50)
	2016			MEP (M: 12.80)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
36 in Taiwan	2013-2016	7-11 years old	336	MEP (M: 16.77)
		12-17 years old	257	MEP (M: 14.60)
		18-39 years old	356	MEP (M: 19.73)
		40-64 years old	556	MEP (M: 17.31)
		≥ 65 years old	352	MEP (M: 22.16)
This study	2019	7-12 years old	136	MEP (M: 5.63)
		13-18 years old	127	MEP (M: 4.44)
		19-64 years old	622	MEP (M: 5.11)
		≥ 65 years old	690	MEP (M: 5.74)
BBzP metabolites				
Lin et al. 2011 in Tainan	2000-2001	Pregnant women	155	MBzP (M: 15.60)
Lin et al. 2011 in Taichung	2005-2006	Pregnant women	99	MBzP (M: 2.07)
		Children at 5 years old	59	MBzP (M: 7.64)
		Children at 2 years old	26	MBzP (M: 11.25)
Huang et al., 2007 in Tainan	2005-2006	Pregnant women	76	MBzP (M: 3.70)
Kuo et al., 2015 in Kaohsiung	2009-2010	Pregnant women	148	MBzP (M: 1.35)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
Huang et al., 2017 in Taipei	2010	Pregnant women	112	MBzP (M: 2.22)
Wu et al., 2018 in northern, central, and southern Taiwan	2012-2013	Children ≤ 12 years old	224	MBzP (M: 2.84)
Tsai et al., 2016 in Taipei, Taichung and Kaohsiung	2012-2013	Children ≤ 18 years old	240	MBzP (M: 10.81)
Wu et al., 2017 in Taiwan	2012-2015	Pregnant women	1631	MBzP (M: 0.47)
	2012-2013			MBzP (M: 2.85)
Huang et al., 2020 in Taiwan	2014-2015	Children at 2-14 years old	166	MBzP (M: 1.53)
	2016			MBzP (M: 1.15)
36 in Taiwan	2013-2016	7-11 years old	336	MBzP (M: 1.55)
		12-17 years old	257	MBzP (M: 1.16)
		18-39 years old	356	MBzP (M: 0.83)
		40-64 years old	556	MBzP (M: ND)
		≥ 65 years old	352	MBzP (M: ND)

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Studies and Location	Sampling year	Target group	Number of participants	Phthalate metabolites concentration (μg/g cr.)
This study	2019	7-12 years old	136	MBzP (M: 0.42)
		13-18 years old	127	MBzP (M: 0.29)
		19-64 years old	622	MBzP (M: 0.45)
		≥ 65 years old	690	MBzP (M: 0.64)

M: Median; MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate

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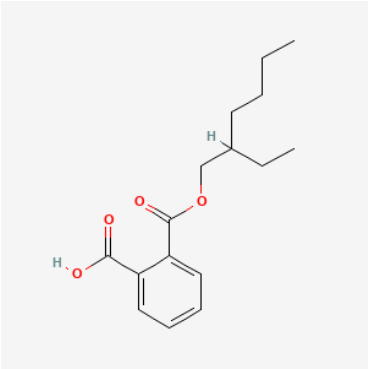
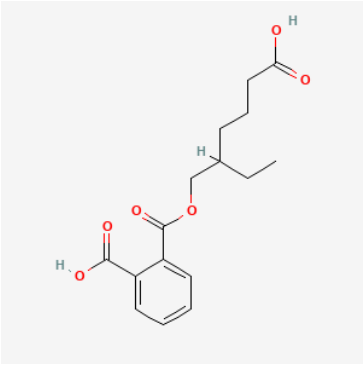
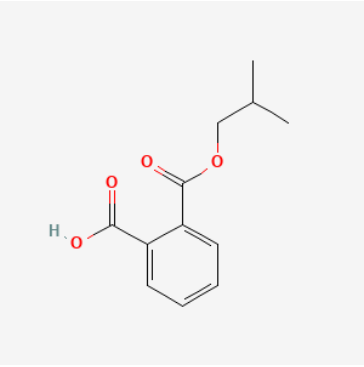
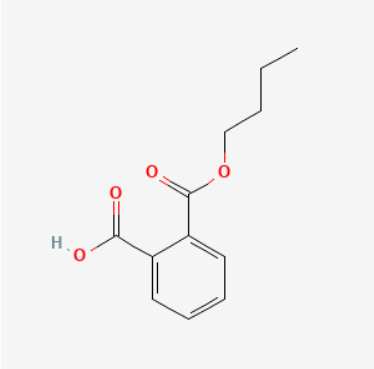
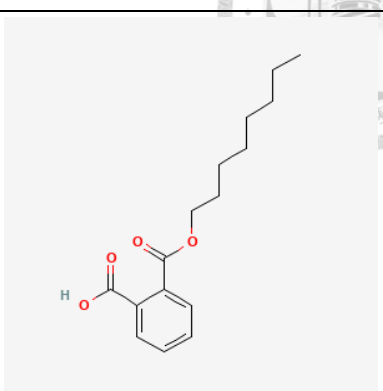
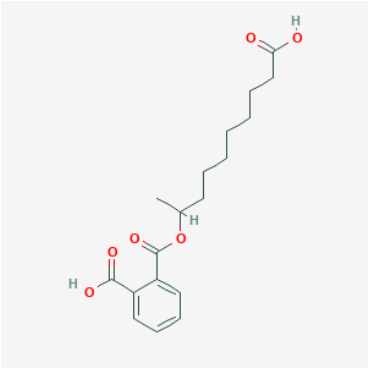
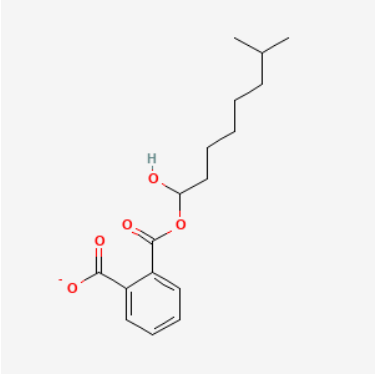
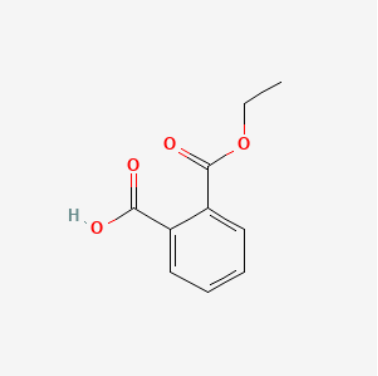
Supplements

Table S1. Chemical structures and molecular weights of analytes.

Compounds	Molecular weights	Structures
Mono(2-ethylhexyl) phthalate (MEHP)	278.34	
Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)	308.33	
Mono-iso-butyl phthalate (MiBP)	222.24	
Mono-n-butyl phthalate (MnBP)	222.24	

doi:10.6342/NTU202301080

Compounds	Molecular weights	Structures
Mono-n-octyl phthalate (MnOP)	278.34	
Mono-carboxyisononyl phthalate (MCINP)	336.4	
Mono-hydroxyisononyl phthalate (MHINP)	307.4	
Mono-ethyl phthalate (MEP)	194.18	

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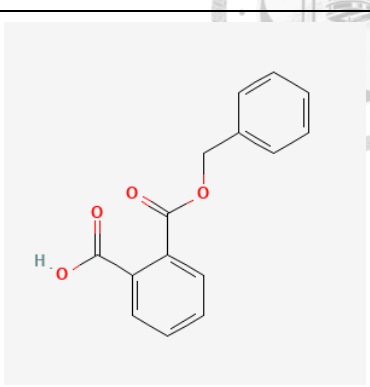
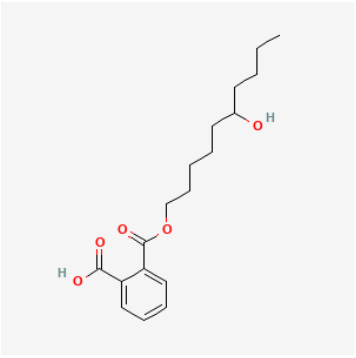
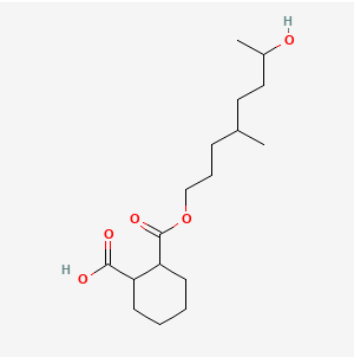
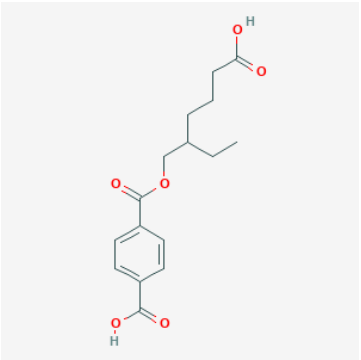
Compounds	Molecular weights	Structures
Mono-benzyl phthalate (MBzP)	256.25	
Mono-2-propyl-6-oxo-heptyl phthalate (oxo-MPHP)	322.4	
Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester (OH-MINCH)	314.4	
Mono-2-ethyl-5-carboxypentyl Terephthalate (MECPTP)	308.33	

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Table S2. Retention time, Limit of Detection (LOD), limit of quantification (LOQ), linear range and r^2 of each phthalate metabolites (pg/ml) analysis.

Compounds	Retention time (min)	LOD ± SD (pg/mL)	LOQ ± SD (pg/mL)	Linear range (ng/mL)	r^2
MnBP	3.90	156 ± 30.9	433 ± 85.3	1-500	0.993
MiBP	3.82	203 ± 50.0	376 ± 59.0	1-500	0.991
MnOP	6.30	95.4 ± 7.21	238 ± 50.2	0.5-500	0.998
oxo-MPHP	4.91	87.5 ± 24.5	195 ± 36.5	0.5-500	0.998
MHINP	4.66	553 ± 147	553 ± 147	0.5-500	0.998
MCINP	5.76	133 ± 40.3	179 ± 37.9	0.5-500	0.998
MEHP	6.14	51.9 ± 31.1	263 ± 96.5	1-500	0.999
MECPP	4.97	721 ± 308	721 ± 308	1-500	0.997
OH-MINCH	5.50	330 ± 72.6	330 ± 72.6	0.5-500	0.996
MEP	1.79	2313 ± 286	2313 ± 286	2-500	0.997
MBzP	4.17	482 ± 81.5	482 ± 81.5	0.5-500	0.996
MECPTP	5.52	137 ± 12.9	245 ± 36.5	0.5-500	0.998

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MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

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Table S3. Tandem mass parameters.

Phthalate metabolites	Cone voltage (V)	Ion transition (m/z) (collision energy, V)	Internal standard	Cone voltage (V)	Ion transition (m/z) (collision energy, V)
MnBP	15	221.1 >76.8 (15), 71.3 (14)	MnBP-$^{13}C_4$	20	225.2 > 78.9 (20)
MiBP	20	221.0 > 77.0 (16), 134.0 (16)			
MnOP	20	277.2 > 126.9 (15), 76.8 (20)	MnOP-D_4	10	281.2 > 126.9 (15)
oxo-MPHP	15	319.3 > 121.0 (20), 171.0 (15)	oxo-MPHP-$^{13}C_4$	15	323.4 > 123.9 (20)
MHINP	25	307.2 >120.8 (15), 158.9 (15)	MHINP-D_4	5	311.0 > 124.8 (15)
MCINP	2	335.2 > 187.2 (16), 121.2 (24)	MCINP-D_4	10	339.3 > 187.2 (15)
MEHP	25	277.3 > 127.1 (15), 77.0 (15)	MEHP-$^{13}C_4$	25	281.3 >136.8 (16)
MECPP	2	307.1 >159.2 (14), 113.2 (28)	MECPP-$^{13}C_4$	18	311.3 > 159.1 (11)
OH-MINCH	15	313.1 > 152.8 (20), 109.0 (20)	OH-MINCH-D_8	40	321.2 > 160.9 (20)
MEP	30	193.0 > 77.0 (25), 121.0 (15)	MEP-$^{13}C_4$	5	197.0 > 78.9 (15)
MBzP	4	255.1 > 77.0 (20), 183.1 (12)	MBzP-$^{13}C_4$	30	259.1 > 165.0 (15)
MECPTP	25	307.1 > 165.0 (15), 121.0 (15)	MECPTP-D_4	30	311.1 > 168.8 (15)

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MEP: Mono-ethyl phthalate; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

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Table S4. Geometric mean, minimum, maximum, and selected percentiles of phthalate metabolites levels (μg/L) in Taiwan HBM 2019 study.

	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
Phthalates (μg/L)										
MEP										
7-12 yrs	136	71.32%	6.41 (5.16-7.96)	1.63	1.63	5.15	15.80	58.70	431.80	
13-18 yrs	127	81.10%	7.46 (5.99-9.28)	1.63	2.80	6.00	14.60	71.20	328.30	<0.001***
19-64 yrs	622	64.31%	5.74 (5.15-6.39)	1.63	1.63	4.00	12.53	86.86	1349.07	
≥ 65 yrs	690	56.09%	4.75 (4.28-5.27)	1.63	1.63	2.93	9.48	95.82	2248.05	
MnBP										
7-12 yrs	136	100%	13.22 (11.95-15.60)	1.40	6.80	13.35	27.15	72.90	126.70	
13-18 yrs	127	100%	10.88 (9.31-12.71)	1.60	5.80	11.10	20.00	49.20	95.80	<0.001***
19-64 yrs	622	99.84%	5.23 (4.82-5.67)	0.07	2.47	4.74	9.58	35.27	217.86	
≥ 65 yrs	690	100%	4.41 (4.08-4.77)	0.29	2.09	3.83	8.37	32.00	262.54	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MiBP										
7-12 yrs	136	100%	6.30 (5.32-7.47)	0.80	3.30	5.25	11.65	47.10	222.20	
13-18 yrs	127	100%	4.99 (4.27-5.83)	0.90	2.70	4.70	8.20	21.70	126.50	
19-64 yrs	622	100%	2.42 (2.25-2.61)	0.22	1.25	2.19	4.20	14.08	2376.73	<0.001***
≥ 65 yrs	690	100%	1.83 (1.72-1.95)	0.32	0.98	1.68	3.11	7.98	87.20	
MEHP										
7-12 yrs	136	100%	3.78 (3.24-4.40)	0.50	2.00	3.35	7.15	18.90	41.00	
13-18 yrs	127	100%	3.07 (2.71-3.47)	0.60	1.90	3.20	5.20	8.60	17.00	
19-64 yrs	622	99.84%	2.03 (1.90-2.17)	0.03	1.11	1.84	3.69	9.73	28.27	<0.001***
≥ 65 yrs	690	100%	1.73 (1.62-1.84)	0.06	1.01	1.54	3.00	8.07	32.43	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MECPP										
7-12 yrs	136	100%	15.85 (13.74-18.28)	2.70	9.15	13.75	27.70	81.10	185.80	
13-18 yrs	127	100%	11.37 (9.89-13.08)	1.33	6.40	11.00	16.90	46.00	103.90	
19-64 yrs	622	98.71%	5.50 (5.12-5.90)	0.51	3.02	5.34	9.85	22.94	358.00	<0.001***
≥ 65 yrs	690	98.84%	5.00 (4.69-5.33)	0.51	2.91	4.83	8.76	19.96	232.09	
MBzP										
7-12 yrs	136	28.67%	0.46 (0.42-0.51)	0.34	0.34	0.34	0.50	1.90	8.00	
13-18 yrs	127	27.56%	0.46 (0.41-0.52)	0.34	0.34	0.34	0.50	1.40	20.50	
19-64 yrs	622	12.06%	0.39 (0.38-0.40)	0.34	0.34	0.34	0.34	0.87	13.37	<0.001***
≥ 65 yrs	690	12.46%	0.39 (0.38-0.40)	0.34	0.34	0.34	0.34	0.95	6.45	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MnOP										
7-12 yrs	136	70.59%	0.15 (0.13-0.18)	0.07	0.07	.010	0.20	0.90	5.90	
13-18 yrs	127	63.78%	0.11 (0.10-0.13)	0.07	0.07	0.10	0.15	0.47	0.90	
										<0.001***
19-64 yrs	622	44.86%	0.14 (0.13-0.15)	0.07	0.07	0.07	0.26	0.94	5.13	
≥ 65 yrs	690	37.97%	0.13 (0.12-0.14)	0.07	0.07	0.07	0.20	0.83	2.91	
MHINP										
7-12 yrs	136	99.26%	4.28 (3.58-5.12)	0.39	2.20	3.80	7.65	26.30	411.90	
13-18 yrs	127	94.49%	3.82 (3.13-4.67)	0.39	1.70	3.40	8.50	21.10	163.60	
										<0.001***
19-64 yrs	622	66.08%	1.00 (0.92-1.08)	0.39	0.39	0.77	1.79	6.12	239.59	
≥ 65 yrs	690	57.54%	0.80 (0.75-0.86)	0.39	0.39	0.63	1.22	4.33	300.65	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
MCINP										
7-12 yrs	136	86.03%	0.39 (0.34-0.46)	0.09	0.20	0.40	0.70	2.20	16.00	
13-18 yrs	127	80.31%	0.31 (0.27-0.36)	0.09	0.20	0.30	0.50	1.20	9.90	
19-64 yrs	622	40.51%	0.13 (0.12-0.14)	0.09	0.09	0.09	0.18	0.39	58.10	<0.001***
≥ 65 yrs	690	31.88%	0.12 (0.11-0.13)	0.09	0.09	0.09	0.16	0.37	1.67	
oxo-MPHP										
7-12 yrs	136	100%	1.02 (0.88-1.17)	0.20	0.59	0.90	1.65	4.70	19.00	
13-18 yrs	127	100%	1.00 (0.85-1.17)	0.20	0.50	1.00	1.50	3.70	453.50	
19-64 yrs	622	100%	0.48 (0.45-0.52)	0.09	0.25	0.41	0.78	2.17	1417.96	<0.001***
≥ 65 yrs	690	100%	0.44 (0.41-0.47)	0.10	0.23	0.37	0.67	2.13	36.24	

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	N	> LOD (%) [a]	GM (95% CI)	Min	Selected percentiles				Max	*p*-values [b]
					25th	50th	75th	95th		
OH-MINCH										
7-12 yrs	136	71.32%	0.79 (0.65-0.95)	0.23	0.23	0.60	1.65	7.20	26.30	
13-18 yrs	127	64.57%	0.62 (0.51-0.74)	0.23	0.23	0.50	1.00	5.30	29.80	
19-64 yrs	622	32.96%	0.39 (0.36-0.42)	0.23	0.23	0.23	0.47	4.12	62.54	<0.001***
≥ 65 yrs	690	31.16%	0.38 (0.36-0.41)	0.23	0.23	0.23	0.46	2.87	94.15	
MECPTP										
7-12 yrs	136	100%	3.03 (2.50-3.67)	0.30	1.55	2.90	4.75	23.50	686.20	
13-18 yrs	127	100%	2.69 (2.17-3.34)	0.30	1.20	2.30	5.00	29.70	223.70	
19-64 yrs	622	95.66%	1.47 (1.30-1.66)	0.10	0.55	1.17	3.28	32.41	1003.93	<0.001***
≥ 65 yrs	690	93.19%	1.09 (0.98-1.21)	0.10	0.41	0.91	2.37	16.92	2676.87	

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HBM: Human biological monitoring; LOD: Low of detection; GM: geometric mean; MEP: Mono-ethyl phthalate ; MiBP: Mono-iso-butyl phthalate; MnBP: Mono-n-butyl phthalate; MEHP: Mono(2-ethylhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; MBzP: Mono-benzyl phthalate; MnOP: Mono-n-octyl phthalate; MCINP: Mono-carboxyisononyl phthalate; MHINP: Mono-hydroxyisononyl phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. LOD data were calculated $1/\sqrt{2}$ of detection limit.

b. Comparison of age group by Mann–Whitney U test and Kruskal-Wallis test. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

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Table S5. Human biomonitoring guidance values for the general population (HBM-GV_{GenPop}), HBM-I value and Tolerable Daily Intake (TDI) derived for selected phthalates and substitutes.

Parent compound	TDI (mg/kg bw/day)	Metabolites	HBM-I value (μg/L)			HBM-GV_{GenPop} (μg/L)	
			Children [a]	Adolescents and adults	Women of child-bearing age	Children [a]	Adolescents and adults [b]
DEHP	0.05	5-oxo-MEHP + 5-OHMEHP	500	750	300	340	500
		MECPP + 5-OHMEHP	-	-	-	380	570
DnBP	0.01	MnBP	-	-	-	120	190
DiBP		MiBP	-	-	-	160	230
BBzP	0.50	MBzP	-	-	-	2000	3000
DPHP	- [d]	oxo-MPHP + OH-MPHP	1000	1500	-	330	500
DINCH	-	OH-MINCH + cx-MINCH	3000	4500	-	3000	4500
DEHTP	-	MECPTP	1800	2800	-	-	-

DEHP: di (2-ethylhexyl) phthalate;5-oxo-MEHP: Mono(2-ethyl-5-oxohexyl) phthalate; 5-OHMEHP: Mono(2-ethyl-5-hydroxyhexyl) phthalate; MECPP: Mono(2-ethyl-5-carboxypentyl) phthalate; DnBP: Di-n-butyl phthalate; MnBP: Mono-n-butyl phthalate; DiBP: di-iso-butyl phthalate;

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MiBP: Mono-iso-butyl phthalate; BBzP: butyl benzyl phthalate; MBzP: Mono-benzyl phthalate; DPHP: di-(2-propylheptyl) phthalate; oxo-MPHP: Mono-2-propyl-6-oxo-heptyl phthalate; DINCH: di-iso-nonyl-cyclohexane-1,2-dicarboxylate; OH-MINCH: Cyclohexane-1,2-dicarboxylic acid-mono(hydroxyisononyl) ester; cx-MINCH: Cyclohexane-1,2-dicarboxylate-mono-(7-carboxylate-4-methyl) heptyl ester; DEHTP: di-2-ethylhexyl terephthalate; MECPTP: Mono-2-ethyl-5-carboxypentyl Terephthalate.

a. Including children 6–13 years of age.
b. Including women of child-bearing age.
c. HBM-GVs data taken from Lange et al., 2021; HBM-I value data taken from Apel et al., 2017; TDI data taken from Taiwan Environmental Protection Administration Executive Yuan, 2011.
d. Data not reported.

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