

Review

Phthalic acid derivatives: Sources and effects on the human body

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Abstract: The review summarizes data on the sources of phthalates in the environment and the routes of their penetration into the human body (food and inhalation routes are described in detail). The article discusses methods for detecting phthalates in the human body and assessing adverse effects. Up-to-date information on the effects of phthalic acid derivatives on the human body is presented, potential health risks for people of different age groups are highlighted. Particular attention is paid to the adverse effects of phthalate derivatives on the respiratory system, especially in the context of inhalation of suspended particles contained in the atmospheric air.

Keywords: phthalates, dibutyl phthalate, diisobutyl phthalate, diethylhexyl phthalate, PM2.5, toxic effect.

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Background

Phthalates are among the most commonly encountered chemicals in everyday life. Their widespread use has led to a growing body of evidence indicating that consumers in industrialized countries are exposed to phthalates in a variety of ways [1, 2]. Phthalates are widely used as plasticizers in a number of industries (factory production of medical devices, construction materials, cosmetics, etc.) [3, 4]. Phthalates are added as plasticizers to plastics, in the production of polyvinyl chloride (PVC), polystyrene, synthetic and natural rubber, and in various consumer products due to their low cost, attractive properties, and lack of suitable alternatives [5, 6]. Phthalates are found in households and industrial settings [7] and are ubiquitous contaminants of food and the environment [8, 9]. In everyday life, people encounter these materials in a variety of contexts, including children's toys, floor coverings (linoleum, laminate) [10], finishing materials (washable wallpaper, paints, varnishes), furniture, plastic tableware [11-14], shoes and clothes made of artificial leather and synthetic fabrics, syringes, blood containers, drug capsules, packaging materials, repellents, perfumes and many other products [15].

All studied phthalates are classified as highly hazardous compounds (Hazard Class 2). Due to their prevalence and general availability, as well as the multiple routes of their penetration into the human body, it is inevitable that people encounter them in everyday life [16]. Based on the various routes of exposure, including ingestion, drinking water, dust/soil, air inhalation and dermal exposure, their daily intake can reach critical levels [17]. Research in recent years has significantly expanded our understanding of the pathogenic effects of phthalic acid derivatives [18]. An analysis of the available literature on the sources and routes of phthalates entering the environment and

their effects on the human body provides a basis for developing strategies in the field of regulating their content in order to reduce the risk of destructive impact on human health. At present, ideas about the pathogenicity of phthalates are significantly expanding. However, among domestic and foreign literature, there are virtually no comprehensive published sources dedicated to the problem of accumulation of phthalic acid esters in the air, including those associated with microparticles.

Sources of phthalates entering the body

Phthalates are so common in the environment that they are virtually invisible chemical actors in our everyday life. They are relatively inexpensive to produce and have high plastic properties, which has led to a surge in their use in recent years. For example, the synthesis of phthalic acid derivatives has exceeded eight million tons per year globally over the past five years [17, 19]. A number of representatives of this class have gained popularity as plasticizers ([Table 1](#)). Phthalates as plasticizers have become so popular that they are used in nearly all types of production. These include the construction industry (PVC, windows, adhesives, floor coverings, wall panels, etc.), the food industry (plastic containers, meat absorbent pads, disposable tableware, etc.), the production of medical equipment (packaging, droppers, tubes), etc. The products of these industries are a significant source of phthalates in the environment ([Figure 1](#)).

Diethylhexyl phthalate (DEHP), dibutyl phthalate (DBP) and diisobutyl phthalate (DIBP) are widely used to soften and increase the flexibility of plastics [12]. Due to the lack of a covalent bond between the phthalate molecules and the polymer, as well as to a low vapor pressure, phthalates are slowly released from plastics into the environment [20]. DEHP, diisononyl phthalate (DINP) and diisodecyl phthalate (DIDP) combined account for over 75% of the

total phthalate consumption in Europe, with an estimated annual emission of more than 3.5 million tons [19].

Routes by which phthalates enter the human body can be classified into two main types: specific and general. Specific route involves the penetration of phthalates into the human body at industrial facilities. In such cases, the toxic effect is acute. It should be noted that the emission of phthalates into the air of industrial premises increases sharply at temperatures above 100 °C. Such conditions are created during the production of building materials, plastics, etc. [7]. In the case of a generally accessible route, which includes food and inhalation routes, the penetration of toxins is systematic, cumulative, and the assessment of their impact on the body is difficult due to the time factor.

One of the most common sources of phthalates entering the body is the consumption of food. Previous studies [20, 21] demonstrated that food is a significant source of DBP and DEHP. Recently, researchers noted that DEHP can migrate from packaging materials into food [22]. For example, DEHP was detected in all olive oil packaging samples in Turkey, with its concentration reaching 602 mg/kg [23]. An increase in the phthalate impact on consumers is also caused by heating food in plastic containers [20]. A special place in this context is occupied by the consumption of bottled water. It has been shown that the presence of plasticizers in drinking water is caused by improper storage and production conditions of plastic containers [21, 24, 25]. Scientists from Jordan conducted a study of water samples from 14 companies offering bottled water. The results showed that all samples contained a mixture of phthalates, including DBP, DEHP and dioctyl phthalate (DOP) in varying proportions. The total content of the above-mentioned phthalates ranged from 8.1 mg/mL to 19.8 mg/mL. The concentration of phthalates increased to a maximum of 29.2 mg/mL when the product was stored for 21 days at a temperature of 50 °C [26]. A study of the phthalate content in drinks produced in Vietnam showed that the quantitative limits ranged from 0.03 to 0.15 ng/mL [27]. A study conducted in Taiwan found that DEHP and diisononyl phthalate (DINP) had been illegally used as a thickening agent-stabilizer for a long period of time. A significant number of food products, including sports drinks, juice drinks, tea drinks, and fruit jams/nectars/jellies, contained these toxic substances [28]. To determine the extent of harm to consumers' health, a follow-up study known as the Exposure Estimation for Risk Assessment of Phthalate Incidence in Taiwan was conducted, which involved thousands of children [29].

In the atmosphere, phthalates pose a significant risk due to their diverse toxicological effects. The inhalation route represents a significant proportion of total exposure, with estimates ranging from 24.3% to 96.8% for dimethyl phthalate (DMP) and from 2.1% to 30% for DEHP [9, 30]. Phthalates tend to accumulate in urban and suburban areas of large urban and industrial agglomerations. Concentrations in isolated areas can be considered background levels. Average air concentrations at Enewetak Atoll were 0.9 ng/m³ for DBP and 1.4 ng/m³ for DEHP. In the Arctic, these values were 543 pg/m³ for DEHP, 139 pg/m³ for DBP, and 20 pg/m³ for diethyl phthalate (DEP). Higher concentrations (annual averages) have been measured in Paris. The mean concentrations of DEHP, DBP and DEP were 17.5±7.7%, 18.4±9.9% and 9.0±6.2% ng/m³, respectively. In Sweden, the mean concentrations of DEHP and DBP ranged from 0.28% to 77.7% ng/m³ and from 0.23% to 49.9% ng/m³, respectively [31].

A study was conducted to assess the concentrations of six of the most common phthalates in North America, Asia and Europe [30]. The results showed that their mean total concentrations in settled dust were 500.02 µg/g in North America, 580.12 µg/g in Europe and 945.45 µg/g in Asia. Meanwhile, DEHP is the most abundant phthalate, with its mean and median values of 615.78 µg/g and 394.03 µg/g, respectively (Table 2). The results of indoor air analysis show that the average concentration of six common phthalates was 598.14 ng/m³ in North America, 823.98 ng/m³ in Europe, and 1710.26 ng/m³ in Asia (Table 3). A study conducted by researchers from China found the presence of phthalates in all dust sediment samples collected from Hangzhou, Taizhou, and Wenzhou Bays [32]. The total phthalate concentrations ranged from 654 to 2,603 ng/g, of which DEHP was the most common chemical (on average, 663 ng/g accounting for 52% of the total toxicants).

It is critical to recognize that phthalates can exist in both condensed and free forms. E.g., DBP and DEHP have different vapor pressures, polarities, and water solubilities. The vapor pressure of DBP is two orders of magnitude greater than that of DEHP, indicating that DBP is predominantly in the gas phase, whereas DEHP is predominantly in the condensed phase (i.e., dust-bound). At particle concentrations greater than 20 µg/m³, DBP is in the gas phase, whereas at concentrations greater than 85 µg/m³, DEHP is bound to airborne particles [33]. The deposition of compounds in the respiratory tract is highly dependent on whether the compound is present in the gas phase or bound to airborne particles. The relative partitioning between the gas and condensed phases, combined with individual toxicological and pharmacokinetic characteristics, contribute to phthalates triggering various health effects depending on their structure [7]. The sorption process occurring in a variety of settings including outdoor air, indoor air, and air in between the two environments, as well as between the human body and outdoor air, was extensively investigated in a series of papers by Weschler et al. [7, 34-36]. The interphase partitioning of polycyclic volatile compounds in outdoor air, the residence time of organic compounds indoors and the dependence of individual health effects on the interphase and intersurface partitioning of these substances are also presented in the study by Zannoni N. et al., 2021 [37]. The results of the studies by Abbate J.P.D. et al. (2021) [38] and He L. et al. (2023) [39] confirmed that low molecular weight phthalates were more abundant in the gaseous state than high molecular weight phthalate, which were mainly deposited on particles and surfaces.

Table 1. Phthalates most commonly used as plasticizers that pose the greatest risk to the human body. Abbreviated form of phthalates

<i>Phthalates with an aliphatic chain of up to 6 atoms</i>	<i>Phthalates with an aliphatic chain of more than 6 atoms</i>
DMP – dimethyl phthalate	DHPH – bis(2-propylheptyl) phthalate
DEP – diethyl phthalate	DOP – dioctyl phthalate
DBP – dibutyl phthalate	DIOP – diisooctyl phthalate
DIBP – diisobutyl phthalate	DNP – dinonyl phthalate
BBP – benzyl butyl phthalate	DINP – diisononyl phthalate
DEHP – diethylhexyl phthalate	DIDP – diisodecyl phthalate

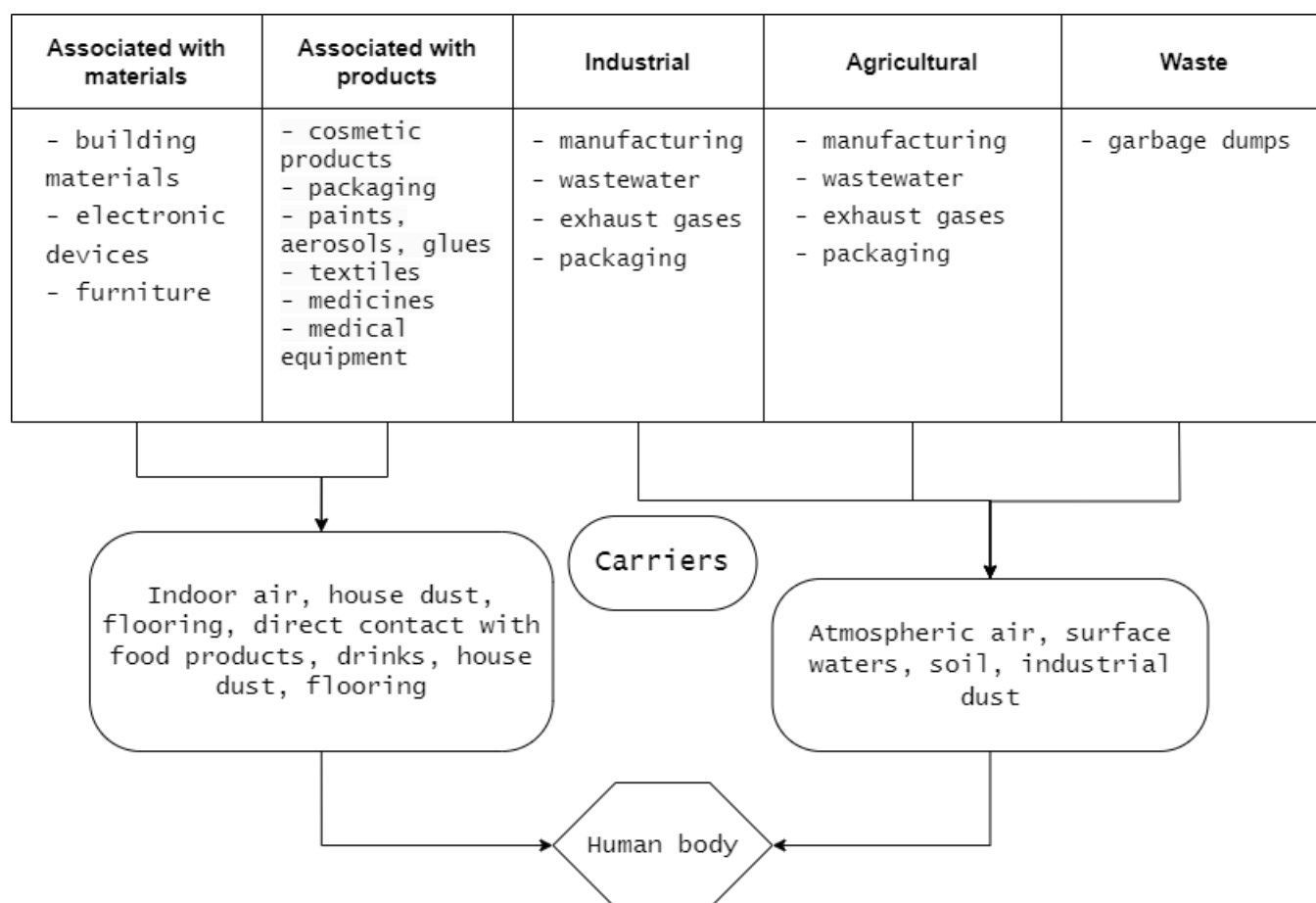


Figure 1. Sources of phthalates entering the human body.

Table 2. Percentage of individual phthalates from their total amount in dust

Country	DMP	DEP	DIBP	DBP	DEHP	BBP
Vietnam	-	-	5.5	5.5	86	3
Japan	-	2	-	3	93.5	1.5
Sweden	-	2.5	12	14.5	63	6
Germany	-	-	5.5	7	86.3	1.2
France	-	2.2	8	5.5	81.3	3
USA	2.8	1.8	5	10.5	61.9	18
China	1.4	2	6.7	16.4	73.5	<1

Table 3. Percentage of each phthalate from their total amount in indoor air (both in the gaseous phase and in the adsorbed form on particles)

Country	DMP	DEP	DIBP	DBP	DEHP	BBP
Vietnam	4.5	18.5	29	14	33	1
Japan	6	9	14	46	23.5	1.5
Sweden	1.5	31.5	20	25	19	1
Germany	12	17	16	38	17	<1
France	4.5	25.5	40.5	14	5	<1
USA	4	53	11	16	7	2
China	16.5	12	14	20.5	17.5	19.5

Indoors, the main sources of phthalate exposure among all consumer groups are PVC materials. A correlation was established between the presence of PVC flooring and the presence of DEHP and DBP vapors [7, 39]. Importantly, there is a potential link between persistent allergic symptoms, which have increased markedly in developed countries over the past three decades, and phthalate concentrations in house dust. A series of studies

demonstrated a correlation between phthalate ester concentrations in dust and the prevalence of asthma, rhinitis, and eczema [40]. It was noted that the average DBP concentration in dust was higher in the homes of patients with allergies than in healthy individuals. The analysis demonstrated a correlation between elevated DBP levels and the incidence of rhinitis and eczema, while increased DEHP levels were associated with a higher risk of asthma [41].

The presence of toxicants in the indoor air of child care institutions in Russia is a matter of serious concern. In this context, Ulanova [42] presented the results of a study on phthalate levels in the air of preschools and schools and phthalate metabolites in children attending these institutions. The results showed that the priority pollutants of indoor air in preschools and schools were DBP and DEHP. These phthalates were detected in 11-42% of indoor air samples in preschools and in 6-53% of indoor air samples in schools. The presence of monomethyl phthalate (MMP), monobutyl phthalate (MBP) and, in some cases, monoethylhexyl phthalate (MEHP) was detected in the urine of children attending the studied institutions. The presence of phthalates in indoor and outdoor air implied the possibility of chronic health effects on children via inhaled air. The observed statistically significant correlations between urinary phthalate metabolite concentrations and biological responses suggested adverse health effects of phthalates in children through chronic inhalation exposure.

Table 4. Phthalates metabolites used as markers in the analysis of human biological fluids

Phthalates	Metabolites
DMP – dimethyl phthalate	MMP – monomethyl phthalate
DEP – diethyl phthalate	MEP – monoethyl phthalate
DBP – dibutyl phthalate	Mono-n-butyl phthalate, mono(3-hydroxybutyl) phthalate
DIBP – diisobutyl phthalate	MIBP – monoisobutyl phthalate
BBP – benzyl butyl phthalate	Monobenzyl phthalate, mono(3-hydroxypropyl) phthalate
DEHP – diethylhexyl phthalate	Mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-carboxypentyl) phthalate, mono(2-carboxymethylhexyl) phthalate
DOP – dioctyl phthalate	Mono-n-octyl phthalate, mono(3-carboxypropyl) phthalate
DNP – dinonyl phthalate	Mono-n-nonyl phthalate, monocarboxyoctyl phthalate
DINP – diisononyl phthalate	Monoisononyl phthalate, mono-carboxy-isoctyl phthalate
DIDP – diisodecyl phthalate	Monoisodecyl phthalate, mono-carboxy-isononyl phthalate

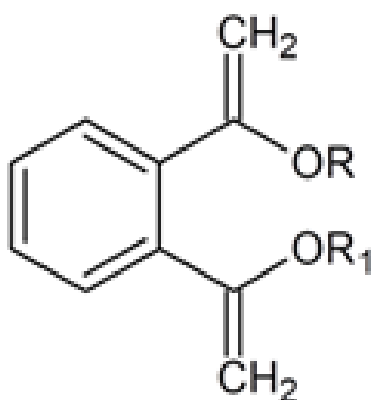


Figure 2. Structure of mono- and diphtalates. $R_1=H$, $R=(CH_2)_nCH_3$ – monoethyl phthalate; $R_1=R=(CH_2)_nCH_3$ – diethyl phthalate.

PM2.5-bound phthalates

Suspended particulate matter (SPM) is an important indicator of air pollution. Particles smaller than 10 μm have been shown to impose the most pathogenic effects on the human respiratory system [2, 43]. There is growing evidence that exposure to microparticles is associated with increased morbidity and mortality in patients with respiratory diseases, as well as aggravation of disease symptoms. Particles with a diameter equal to or smaller than PM2.5 constituting the SPM are capable of penetrating not only the respiratory tract and lungs, but also the systemic circulation. Besides that, airborne toxicants pose a significant hazard when associated with microparticles because they can penetrate deeply into the human respiratory system [44-47]. Therefore, it seems relevant to study the content of phthalates in the urban atmosphere as part of SPM and their pathogenic effects on different groups of the population.

China is among the largest consumers of phthalates globally, and therefore the content of these chemicals in the air of large Chinese cities has attracted the attention of researchers. Exposure assessment showed that inhalation is an important route of phthalate intake. Researchers from China collected samples of PM2.5 particles in large metropolitan areas. The estimated daily intake, risk ratio and index, as well as the possible life expectancy at average daily doses of phthalates and additional lifetime risks of developing cancer for four age groups (infants, toddlers, adolescents and adults) were calculated. To estimate these values, the intake of inhaled particles was taken into account. The four main components detected in the PM2.5 samples were dimethyl phthalate DMP, DEP, DBP and DEHP. The total concentrations of DMP, DEP, DBP, and DEHP in Guangzhou, Shanghai, Beijing, and

Harbin ranged 32.5-76.1 ng/m^3 , 10.1-101 ng/m^3 , 8.02-13.5 ng/m^3 , and 13.5-622 ng/m^3 , respectively. The mean concentrations in these cities were 59.1 ng/m^3 , 50.8 ng/m^3 , 43.8 ng/m^3 , and 136 ng/m^3 , respectively. The total concentrations of phthalates were significantly higher in the warm season than in the cold season. In Harbin, the concentrations of DBP and DEHP were $1.2 \cdot 10^{-6}$ ng/m^3 and $1.3 \cdot 10^{-6}$ ng/m^3 , respectively, which significantly exceeded the permissible level [48].

A comparative study of phthalates associated with PM2.5 particles in samples collected from different types of environments, including student dormitories, office buildings and residential buildings, is of particular interest. Total phthalate concentrations at these sites were 468 ng/m^3 (range 9.52-1,460 ng/m^3), 498 ng/m^3 (11.2-4,790 ng/m^3), 280 ng/m^3 (4.08-1,060 ng/m^3) and 125 ng/m^3 (4.10-4,000 ng/m^3), respectively. The most abundant substances at all sampling sites were DBP and DEHP, accounting for 76.3% and 97.7% of the total analyzed PM2.5-bound substances. The daily inhalation exposure for infants, students and employees was 5.0 mg/kg, 0.8 mg/kg and 0.9 mg/kg of body weight per day, respectively. DBP and DEHP concentrations were significantly higher indoors than outdoors. It was noted that there were clear seasonal variations in cumulative concentrations at all sampling sites. Principal component analysis showed that cosmetics, personal care products, plasticizers and PVC products could be significant sources of PM2.5-bound phthalates [43].

A similar PM2.5 monitoring study assessing exposure in the middle-aged population was conducted in Hong Kong [2]. Air sampling was performed in both residential settings and outdoor areas. Identification of six phthalate esters (DMP, DEP, DBP, benzyl butyl phthalate [BBP], DEHP and DOP) associated with PM2.5 particles was carried out using thermal desorption gas chromatography/mass spectrometry. The mean concentrations of total phthalates in PM2.5 (699.4 ng/m^3) were similar to those in residential areas (646.9 ng/m^3) and lower than those in outdoor areas (1,549 ng/m^3). DEHP was also the most abundant phthalate, with its concentration of 80.3–85.0% detected in all samples, followed by BBP, DBP and DOP. Principal component analysis demonstrated heterogeneous distribution and statistically significant differences in the sources of phthalates across exposure categories. For example, in Hong Kong, for adults, the mean daily inhalation exposures of total phthalates and DEHP were 0.14-0.17 $\mu g/kg/day$ and 0.12-0.16 $\mu g/kg/day$, respectively. A model was constructed to estimate the effect of total phthalates taking into account a time-dependent exposure factor, covering both indoor and outdoor phthalate exposures. The estimated inhalation cancer risk exceeded the US EPA permissible value (1×10^{-6} $\mu g/kg$). These

findings indicate that both outdoor and indoor sources of toxicants should be considered when assessing inhalation health risks.

Similar studies have not yet been conducted in the Russian Federation. The authors carried out studies of the ground-level air in the city of Vladivostok (Primorsky Krai, Russia). For the first time, it was shown that the dominant components of the mixture of substances contained on particles of PM_{2.5} or smaller in the study area were DBP, DIBP, and DEHP [49].

The obtained results suggest that air pollution with phthalates in suspended microparticles in urban areas should be of particular concern and require monitoring studies.

Toxic effects of phthalates on the human body

Phthalic acid derivatives are classified into two categories: those containing up to six atoms and those containing more than six atoms. The former are more dangerous due to their high toxicity to the human body. When ingested once, the substances are not dangerous, but repeated exposure leads to their accumulation, causing chronic intoxication and has a polytropic effect with damage to organs and systems. Children and pregnant women are most vulnerable to the effects of these chemicals. A study conducted in Europe revealed that 17% of children and young adults were at risk of simultaneous exposure to five reprotoxic phthalates: viz., DBP, DIBP, BBP, bis(2-propylheptyl) phthalate (DPHP), and DEHP [6].

After entering the human body, phthalates are hydrolyzed to monoesters [50], which are then further metabolized and excreted in the urine and feces [51]. Quantitative determination of these metabolites (Table 4, Figure 2) allows analyzing the extent of damage to the body. Experimental studies and a literature review have demonstrated that phthalates can remain in the body as metabolites for up to two days, thereby causing chronic health effects [52].

The most toxic phthalates are DMP and dimethyl terephthalates (DMT). Contact of DMP with eyes can cause chemical damage. Polyneuritis has been found in individuals in constant contact with DMP [53]. Other phthalates are no less dangerous for living organisms, since they have both teratogenic and mutagenic effects. Consequently, it was noted that the introduction of food containing DBP and DEHP to pregnant female rats leads to an increased incidence of prenatal fetal death, decreased fetal weight, and the occurrence of birth defects [54]. Exposure to DBP can result in a number of adverse effects including autonomic vascular disorders, asthenia, headache, heavy-headedness, decreased performance, and disorders of memory, attention and sleep. In some cases, menstrual irregularities, a reduction in the number of pregnancies and an increase in the number of spontaneous abortions have been observed [55]. DEHP is a readily available chemical compound that can enter the body with food, inhaled air or through the skin [56]. DEHP has been shown to disrupt the endocrine system. Its destructive effects on the male reproductive system [57], along with hepatorenal and endocrine systems [58], have been noted. Its toxic effects also extend to the nervous system, affecting brain development, especially the hippocampus [59-61]. Epidemiological studies demonstrated an association of exposure to phthalates and their metabolites with diminished sperm count and quality in men, as well as the development of attention deficit disorder symptoms in children [62]. Epidemiological and experimental studies also established that DEHP exposure is positively

correlated with obesity [31, 63-65]. Wiberg was the first to suggest a link between phthalates and atherosclerosis in the elderly in 2014 [66]. The prevalence and echogenicity of carotid plaques were measured in individuals aged 70 years and older, as well as serum concentrations of several phthalates and their metabolites. The results implied that carotid plaque formation was associated with high levels of MMP. Analysis of the data led to the hypothesis, which was confirmed by subsequent studies, that phthalates exert effects on the vasculature, which contributes to the development of atherosclerosis [66, 67]. In a younger group of individuals, a direct association was found of urinary MEHP levels, endothelial microparticles and platelet microparticles (formed as a result of cell death and inflammation) with the development of atherosclerosis. Urinary metabolites of DEHP and MEHP such as mono(2-ethyl-5-oxohexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, and mono(2-ethyl-5-hydroxyhexyl) phthalate were compared with markers of endothelial apoptosis. The results indicated that these markers are involved in the development of atherosclerosis caused by DEHP exposure [68].

Conclusion

The ubiquitous and polytropic nature of phthalates plays an important role in their adverse effects on human health. Analysis of the latest literature provides strong evidence that phthalate derivatives are widely distributed in both residential and workplace settings, as well as in ambient air, including the most pathogenic micro-sized particulate matter. One approach to assessing the adverse effects of toxicants is to quantify exposure markers (chemical compounds and their metabolites) in human biological fluids (blood, urine), exhaled air, etc., and their relationship with the body's response. Research in this area can inform future regulatory policies and evidence-based interventions aimed at reducing exposure to hazardous substances and protecting vulnerable categories of the population. It is imperative to prioritize this issue, conduct comprehensive monitoring studies, and carefully track phthalate exposure in the environment. Such an approach will facilitate the development of new effective regulatory strategies and protect the population from the potential risks associated with phthalates.

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