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Possible Effects of Diethyl Phthalate on Cardiovascular System: A Review Article

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ABSTRACT

Background: Several ailments, including cancer and cardiovascular disease, have been linked to today's sedentary lifestyle and unhealthy eating habits. However, environmental toxins have also been linked to this rise in recent decades. Phthalates, a chemical found in plastics, are a concern because of the amount of time people spend in contact with them on a daily basis. Phthalates exposure has been linked to cardiovascular health in several studies, which have already established a favorable correlation with hypertension and atherosclerosis development in adults and some cardiovascular risk factors in kids, pregnant women as well as adults

Objective: Assessment of possible effects of di ethyl phthalate on different functions of cardiovascular system.

Methods: Di ethyl phthalate, and cardiovascular system were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from January 2000 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Cardiovascular health may be adversely affected by phthalate exposure, with changes in blood pressure and the risk of atherosclerosis as well as metabolic syndromes occurring as a result of early childhood and adult exposure.

Keywords: Di ethyl phthalate, Cardiovascular system.

INTRODUCTION

The cardiovascular system (CVS) serves as the body's primary means of transporting nutrients and oxygen throughout the body. A vital function of the circulatory system is to transport oxygenated blood, essential nutrients, and chemical signals such as hormones throughout the body. In addition, it delivers waste materials such as urea and uric acid to the kidneys for excretion, as well as carbon dioxide through respiratory system. Thermoregulatory control is facilitated in part by CVS. A well-functioning CVS is critical to a person's health and lifespan[(1)].

Cardiovascular system consists mainly of the heart, which is the muscular pumping device simulating man’s closed fist and closed system of vessels including arteries, veins and capillaries. Human heart is a four chambered muscular organ, 2 atria and 2 ventricles. Because of this, the right atrium and ventricle are sometimes referred to as the "right heart" and its left counterparts as the "left heart," respectively, in order to ensure proper blood flow. Four valves; cuspid and semilunar are present in between atria, ventricles and at the base of large vessels to guard the exits of the chambers preventing the backflow of blood[(1)].

Embryologically, in the human body, the heart is the earliest functioning organ to emerge. It is active by the beginning of the 4th week when the placenta is unable to meet the requirements of growing embryo. It arises from the mesodermal layer near the head in a region called cardiogenic area. After that, cardiogenic area begins to develop 2 strands called cardiogenic cords that rapidly form lumen and subsequently referred as cardiogenic tubes[(2)].

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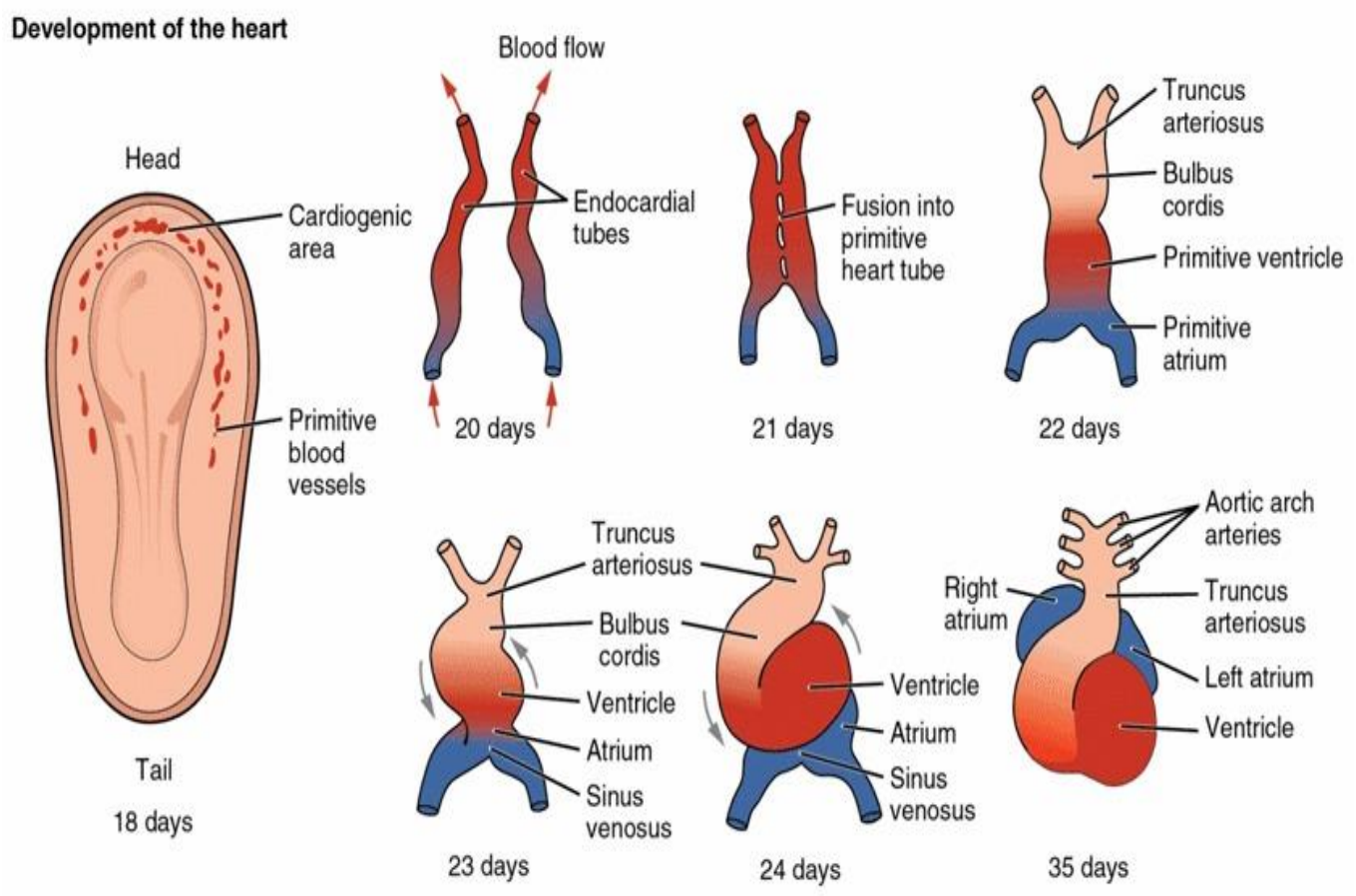

Figure (1): Shows embryonic development of the heart[(2)].

Heart disease is the leading cause of mortality in the world, according to the World Health Organization (WHO). Smoking, sedentary lifestyle, poor eating habits, and diabetes and obesity are all regarded to be major risk factors for these diseases in today's society. As a result, the impact of environmental pollutants on human health has also been suggested as a possible cause of cardiovascular disease (CVD)[(3)].

The most common usage of phthalates is to strengthen polymers and plastics. Due to its low coast, good overall properties and easy processing, phthalate is the most common worldwide plasticizer in polyvinyl chloride plastics (PVC). They are present in hundreds of products as vinyl flooring, lubricating oils, wall covering, floor tiles, and in furniture materials as furniture upholstery and mattresses [(4)].

In addition, food and beverage containers, soft plastic toys, and newborn items all use diethylhexyl phthalate (DEHP) as a raw material, and a range of other consumer goods do as well. Also, DEHP enters in the synthesis of various personal care products as fragrances, deodorants, nail polishes, lotions and hair care products as hair sprays, shampoo and gel. Also, DEHP present in baby care products as oil, lotion, and diaper cream[(5)].

There are eight carbon esters attached to the carbon-benzene dicarboxylic acid chain in the chemical molecule di ethyl phthalate. The molecular weight is 390.56 grams/mol. DEHP is also called bi ethyl hexyl phthalate or dioctyle phthalate. Liquid lipophilic paint remover is more soluble in specific materials like gasoline and oil than it is in water. It is a white viscous liquid. More than two million metric tons of DEHP are generated each year in various parts of the world[(6)].

Polluted air, water, and soil are all signs of misuse of DEHP in industries. DEHP has the ability to attach itself to airborne dust particles and then fall back to Earth. Additionally, it has the ability to form strong bonds with soil. In phthalate contaminated soil, plants can absorb phthalate causing direct damage to human food chain[(7)].

Phthalates are readily absorbed in human body through ingestion, inhalation and also through dermal contact to phthalate contaminated products. In general, ingestion of diet containing DEHP packed foods and bevareges is believed to be the main source of phthalate exposure[(7)].

The amount of DEHP in packed foods depends upon the packing process, the contact time of food with the packing materials, temperature of storage and the lipid content of the packed food. So, packed foods containing high lipid content as milk, butter and processed meat have high concentration of DEHP. Individuals who are used to eat fast foods have higher level of phthalate in urine[(8)].

Dermal absorption is the primary route of non-dietary exposure to DEHP. Dermal exposure is mostly linked to the use of soap, hand cream, toothbrush, wrinkle cream, and shave cream[(9)]. Cheap cosmetics, including hair spray, lotion, sunscreen, deodorant and nail polish

have been linked to an increased risk of phthalate exposure in women[10].

Cardiovascular effects:

Animal Studies:

Only a few of studies have linked DEHP exposure to cardiovascular disease (CVD) in animals. The effects of DEHP on rat cardiomyocyte function have already been documented prior to 2015, resulting to electrophysiological abnormalities in the isolated rat heart and various effects on blood pressure (BP), raising systolic and diastolic pressure in 33-week-old rat juveniles[11].

Since the endothelium-derived NO generation was reduced, it might contribute to the development of CVDs, such as hypertension, if the angiotensin II–AT1R signalling was elevated, which could lead to an increase in BP[12].

DEHP-induced oxidative stress and cardiotoxicity were examined in research by **Amara *et al*.**[13] Authors tested six-week-old male mice intraperitoneally for 30 days with varying dosages of DEHP to see if oxidative damage may cause severe cardiac tissue damages. A considerable rise in both markers was identified as compared to the control group; in fact, malondialdehyde levels were higher in the heart tissue of myocardial damaged mice, indicating an overproduction of reactive oxygen species among these tissues.

There are a few researches showing that phthalates have negative effects on heart function in animal models. A number of genes linked to heart development appear to be affected by phthalates, although the processes behind this are yet unknown. There is a need for further research on the cardiac effects of each phthalate on animals so that human studies on the heart may be developed[13].

Human Studies:

Phthalates have been linked to an increased risk of high blood pressure in children and pregnant women, but there has been just one epidemiological investigation on an adult population in the last several years. A total of 474 Chinese women and men between the ages of 18 and 55 were included in the study, and the levels of 16 different phthalates and lipid profiles in the blood were measured diastolic blood pressure was the most abundant phthalate, with a concentration 59 times greater than that of DEHP. Surprisingly, only di ethyl phthalate was found to raise systolic blood pressure; no other phthalates tested showed any association with diastolic pressure[14].

However, phthalates affect blood pressure in adults, further researches are needed to confirm these findings, especially with diverse populations, in order to examine genetic variability and, primarily, to determine the pathways linked to a rise in blood pressure. A hypothesis for how phthalates cause hypertension has not been presented by the authors, however various possibilities exist. The bradykinin-NO pathway is thought to be inhibited and ACE and AT1R levels increased in rats, leading to hypertension, according to one theory. As a result of insulin resistance, microvascular alterations might occur that could lead to hypertension. Phthalates have been demonstrated to have an effect on heart rate and vascular contraction, which might lead to genetic hypertension can be brought on by modifications in vasoactive components like serotonin or histamine receptors and ion channels that increase responsiveness[14].

Han and colleagues[15] planned research to collect one urine sample every trimester of pregnancy in order to assess the trimester-specific relationship of phthalates throughout pregnancy. Nine phthalates were tested in each spot urine sample supplied by the 633 participants in each of the three trimesters. Maternal blood pressure was found to potentially differ according to the fetus's gender, prompting more stratified investigations. High levels of MiBP exposure in the first trimester were related with elevated BP in the second trimester, however this association was only significant among pregnant women carrying male fetuses.

Unknown mechanisms are thought to be at play, but several hypotheses have been advanced to explain why pregnant women who have been exposed to phthalates have higher blood pressure. Pro-angiogenic substances, such as growth factors, may be released in response to elevated oxidative stress, according to some of these theories, as well as decreased levels of thyroid hormone and an increase in pro-inflammatory cytokines. All of these might have role in the development of gestational hypertension or preeclampsia[15].

On the other hand, the effects of maternal phthalate exposure on the blood pressure and development of children in a Spanish community were studied. Spot urine samples from the first and third trimesters of pregnancy were analysed for phthalate metabolites in 391 mother-child pairs as part of a prospective birth cohort study. The children's blood pressure was tested twice, at ages four and seven, across the study's seven-year span. Decreased systolic blood pressure (but not diastolic blood pressure) was found in girls aged four and seven after exposure to DEHP metabolites and monoethyl phthalate, according to the study's findings[16].

It has been suggested that phthalates may cause cardiometabolic risk through oxidative stress, which is why **Dong and colleagues**[17] opted to investigate the problem in a Shanghai-based diabetic community. Phosphates and oxidative stress indicators in the blood, as well as insulin resistance risk were analysed in this study, which included 300 participants over the age of 50. Oxidative stress may be a factor in the link between phthalates and increased risk of heart disease, diabetes, and cardiovascular disease (CVD), higher risk of cardiovascular disease has been linked to a number of

factors, including the production of androgen hormones, which can cause the metabolic syndrome.

CONCLUSION

Cardiovascular health may be adversely affected by phthalate exposure, with changes in blood pressure and the risk of atherosclerosis as well as metabolic syndromes occurring as a result of early childhood and adult exposure.

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