Introduction
There is growing evidence of the harmful health effects of tobacco smoke. Adverse health effects related to smoking include cardiovascular and respiratory diseases, most notably cancer; furthermore, smoking can affect almost every organ in the body, causing the development of inflammatory bowel disease, skin and mucosal lesions, diabetes type 2, infertility, miscarriage, and low birth weight (1-3). Exposure to environmental tobacco smoke (ETS) among children in their homes has been reported to vary from 27.6% in Africa, 34.3% in Southeast Asia, 50.6% in Western Pacific, and up to 77.8% in Europe (4). ETS has been associated with adverse effects on pediatric health, including preterm birth, intrauterine growth retardation, perinatal mortality, respiratory illness, neurobehavioral problems, and decreased performance in school (5). Tobacco smoke contains numerous toxic properties, namely, more than 5000 compounds among which, at least 69 cases were proved to be carcinogenic (2, 3); some of them are toxic metals. Heavy metals (HMs) represent a group of metallic elements and metalloids characterized by a relative density higher than 5 g/cm³, an atomic number greater than 20, and properties such as the conductance of heat, current, and luster surface (6-8). These elements are naturally present in the environment (air, water, soil, and the like), and due to modern industrialization and urbanization, anthropogenic activities led to increased levels of these metals in the environment. It resulted in high exposure of livings to them (8, 9). The most common HMs in the environment are chromium (Cr), manganese (Mn), nickel (Ni), lead (Pb), cadmium (Cd), copper (Cu), and zinc (Zn). Moreover, the most toxic metalloids are Cr, mercury (Hg), arsenic (As), Cd, Pb, Ni, Cu, and Zn (8). HMs such as As are toxic even for a low level of exposure (10). Regarding their functions in biological systems, HMs can be essential and nonessential. Nonessential HMs do not possess biological functions in living organisms or the metabolic system of plants and animals. This category includes Pb, Cd, Hg, aluminum (Al), and As (8, 11, 12) and exerts toxic effects even at low concentrations (13). Essential HMs are elements that are indispensable for plants and animals and play a vital role in biological processes. They are driving the entire

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Abstract
Metals are a part of trace nutrients necessary for our body. They enter the body and accumulate there in different ways such as drinking water, food, smoking, and the like. In addition, they can lead to harmful health effects. In this study, three databases, including ScienceDirect, PubMed, and Springer, were searched, and articles dealing with the monitoring of metals in human body liquids related to tobacco consumption were selected. The results demonstrated that the total concentration of lead (Pb) and cadmium (Cd) in the hair of children, who were exposed to environmental tobacco smoke (Child E-ETS), was higher than that of children not exposed to tobacco smoke (Child NE-ETS) (4.89 vs. 4.82 µg/g). It was similar for the blood of the children (32.58 vs. 28.3 µg/L). The concentration of Pb, Cd, and arsenic in the blood of adult smokers was significantly higher than that of adult non-smokers (22.07, 1.37, and 22.42 vs. 13.81, 0.57, and 7.51 µg/L). The concentration of the metals in the plasma was higher than the remaining fluids. The concentration of Cd was 0.3286 ± 0.0982 and 0.2759 ± 0.1239 µg/g in the urine of adult smokers and non-smokers, respectively. The results indicated that tobacco smoking could increase some metals in body liquids while decreasing some essential elements of the body, including iron.

Keywords: Lead, Arsenic, Cadmium, Blood, Urine, Breast milk

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The Heavy Metals in Human Body Fluids Related to the Tobacco Smoke: A Systematic Review

Ali Momen, Roohollah Rostami

1Occupational Health Research Center, Department of Occupational Health Engineering, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
2Social Determinants of Health Research Center, Semnan University of Medical Sciences, Semnan, Iran
3Research Center for Health Sciences and Technologies, Semnan University of Medical Sciences, Semnan, Iran

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Heavy metals in human body fluids (e.g., blood, sweat, and urine) and are significantly related to health condition (20-23). For instance, Cu and Zn are essential trace elements that can have detrimental effects on an individual’s health when there is an excess or deficiency (22). High Cu accumulations in the human body can lead to Wilson’s disease (24), heart and kidney failure, liver damage, brain disease and disorder, and even death in extreme cases, whereas low levels of Cu can cause anemia and osteoporosis. A lethal form of diarrhea and pneumonia can occur when a body has low Zn concentrations, whereas high levels of Zn can be toxic enough to cause liver damage and even decrease cardiac functionality and pancreatic enzyme count in the cases of prolonged exposure (22). Regarding the influence of metals on health and the relation of inhaled metals to tobacco smoke, the aim of this study was established to survey the concentration of metals in body fluids and its relationship to tobacco smoking.

**Methods**

In the current systematic review, the databases of Springer, ScienceDirect, and PubMed were searched by applying the keywords of “Heavy metal”, “ETS”, “Tobacco”, “Breast milk”, “Blood”, and “Urine” in the time period from November 1, 2022, to November 27, 2022. The searched term and the results are depicted in Figure 1. In the next step, articles including the words

*Figure 1. Flowchart of the Search and Selection of Articles. Note: ETS: Environmental tobacco smoke*
"Heavy metal" and "Tobacco" or "ETS" in their title or summary or keyword were selected, and 40 articles were selected in this regard. After studying the full papers, 27 articles remained and were included in the current review.

Results

The Concentration of Heavy Metal in Hair
The determination of HMs on hair is one of the methods to know exposure to tobacco smoke. Children exposed to tobacco smoke (Child E-ETS) showed a higher concentration of Pb on their hair than children not exposed to tobacco smoke (Child NE-ETS) (2.43 ± 1.16 vs. 2.33 ± 1.14 µg/g); however, the concentration of As was equal for both of them (0.32 µg/g). Further, adult smokers demonstrated a higher concentration of Pb, Cd, Al, silver (Ag), and Hg on their hair than non-smoker adults, except for Cr (0.045 ± 0.77 vs. 0.077 ± 0.103 µg/g). Furthermore, children who were exposed to tobacco smoke (child E-ETS) were reported to have a higher concentration of Pb than adult smokers (2.43 ± 1.16 vs. 1.98 ± 1.67 µg/g), the details of which are illustrated in Figure 2 (25-27).

The Concentration of Heavy Metals in Blood
HMs enter the body along with smoking and exposure to tobacco smoke and reach different parts of the body by the circulatory system. In this regard, their measurement in the blood is one of the common methods for calculating exposure. Based on the results, the concentration of Pb, Cd, and As in the blood of adult smokers was significantly higher than that of adult non-smokers (22.07 ± 22.32, 1.37 ± 0.79, and 22.42 ± 23.44 vs. 13.81 ± 17.38, 0.57 ± 0.27, and 7.51 ± 6.34 µg/L) (Figure 3). Moreover, the concentration of Pb in the blood of children who were exposed to environmental tobacco smoke (child E-ETS) was higher than that of children who were not exposed to environmental tobacco smoke (NE-ETS), while no significant difference was observed in the concentration of Cd (32.47 ± 12.25 vs. 28.2 ± 9.64 µg/L, 0.11 ± 0.04 vs. 0.1 ± 0.035 µg/L); the obtained data are depicted in Figure 4 (28-39).

The results (Figure 5) revealed that the concentration of As, Pb, and Cd in the blood of smoking pregnant women was higher than that of non-smoking pregnant women (0.83 ± 1.46, 15.19 ± 6.79 and 1.04 ± 0.81 vs. 0.39 ± 0.51, 11.6 ± 2.39, and 0.36 ± 0.12 µg/L) (40, 41).

The Concentration of Heavy Metal in Plasma
Plasma is a part of blood that is often neglected in applications. White blood cells (WBC), red blood cells (RBC), and platelets are essential for body function, but plasma also plays a vital role that is not usually taken into consideration. Plasma transports all the components of the blood in the body. For this reason, plasma is another fluid that can be used for determining the concentration of metals. The results showed (Figure 6) that the concentration of metals in plasma was higher than in other body fluids, and the concentration of these metals was equal for both of them.
in the body of adult smokers was higher than that of non-smokers, except for Se and Fe (83.7 ± 19.1 and 1012 ± 37.4 vs. 154.8 ± 32.9 and 1024 ± 46.2 µg/L) (41-43).

The Concentration of Heavy Metals in the Urine

With exposure to metals, some metals are eliminated by the excretory mechanisms of the body through sweat, urine, feces, and the like. In this regard, the level of exposure to metals can be determined by their measurement in the urine. The results indicated that the concentration of Cd in the urine of adult smokers (0.3286 ± 0.0982 µg/g) was higher than in the adult non-smokers (0.2759 ± 0.1239 µg/g) (32, 33, 37, 44, 45). Additionally, in the urine of children who were exposed to environmental tobacco smoke (child E-ETS), the concentration of Co and Sn was significantly higher than that of children who were not exposed to environmental tobacco smoke (child NE-ETS) (1.09 ± 0.91 and 1.43 ± 1.63 vs. 0.77 ± 0.54 and 1.13 ± 1.44 µg/L), the details of which are shown in Figure 7 (29, 46).

The Concentration of Heavy Metal in Breast Milk

Breast milk is the best food for a newborn. Human milk consists of 87% water, 1% protein, 4% lipid, and 7% carbohydrate (including 1-2.4% oligosaccharides).

It also contains many minerals such as calcium (Ca), phosphorus, magnesium, potassium, sodium, and the like and vitamins (47). Therefore, mother’s milk is especially important among body fluids. In this regard, Szukalska et al conducted a study on the concentration of metals in breast milk and its relationship with smoking. Their results (Figure 8) indicated that the concentration of Cd and Pb in the milk of smoking mothers was significantly higher than that of non-smoking mothers (0.32 ± 0.27 and 3.08 ± 1.47 vs. 0.06 ± 0.03 and 0.815 ± 0.43 µg/L) (48). In another study, Dursun et al investigated the concentration of some metals in cord blood, breast milk, and newborn baby hair. Based on their results, the concentration of Pb in cord blood for mothers who were exposed to environmental tobacco smoke (E-ETS) and mothers who were not exposed to environmental tobacco smoke (NE-ETS) was 16.4 ± 15.5 and 17.4 ± 17.8 µg/L, respectively. Likewise, they reported that the concentration of Pb and mercury (Hg in breast milk for the mothers who were E-ETS and mothers who were NE-
ETS was 14.99 ± 12.11 and 1.41 ± (<DL-7.28) µg/L and 13.29 ± 13.22 and 1.29 ± (<DL-7.99) µg/L, respectively. The concentrations of Pb, Cd, and Hg in the hair of newborn children whose mothers were E-ETS and NE-ETS were 2.72 ± 1.31, 0.24 ± 0.25, and 0.08 ± 0.05 µg/g, as well as 2.71 ± 1.89, 0.21 ± 0.18, and 0.05 ± 0.03 µg/g, respectively (49).

Other Body Fluids

The serum is a part of blood that is similar in composition to plasma but does not contain clotting factors. The components of plasma and serum are similar because they both contain hormones, glucose, electrolytes, antibodies, antigens, nutrients, and some special particles, except for clotting factors that are only present in plasma. Blood serum is one of the body fluids that can be used for measuring the concentration of metals. In this regard, Badea et al. investigated the concentration of metals in the blood serum of smokers and non-smokers. The results showed that smokers had higher concentrations of metals in their serum than people who did not smoke, except for Fe, beryllium, Cd, and Sn (1060.68 ± 569.15, 0.28 ± 0.3, 0.035 ± 0.1 and 4.36 ± 1.2 vs. 1182.7 ± 862.1, 0.75 ± 0.4, 0.04 [IQR = 0], and 8.95 ± 11.7 µg/g, Figure 9 (50).

Saliva is a clear liquid that is secreted by salivary glands. This liquid is one of the most important factors that facilitates swallowing and tasting. Most of the saliva is made up of water. For this reason, one of the ways to detect exposure to foreign substances such as metals is to measure them in the saliva. In this regard, Khabour et al. evaluated metals in the saliva of smokers. The results demonstrated that the concentrations of Pb, Cd, and Zn in the saliva of smokers and non-smokers were 4.8 ± 0.58, 5.1 ± 0.36, and 940 ± 70 µg/L, as well as 2.8 ± 2.7, 0.64 ± 0.2, and 450 ± 60 µg/L, respectively (43).

Discussion

The findings indicated that the concentrations of nicotine and cotinine in hair were positively correlated with Pb, Ag, Cd, and Hg, whereas they were not correlated with Cr (25). HMs enter the body along with smoking and exposure to tobacco smoke and reach different parts of the body through the circulatory system. In this regard, measuring them in the blood is one of the common methods for calculating exposure. It was expected that smoking has an influence on the concentration of Cd and Pb in the blood (31). The blood parameters showed a decrease in RBC and hemoglobin levels that might be linked to the presence of HMs detected in the blood of the exposed individuals. As RBC is generated by the hematopoietic tissues of the kidney/spleen, studies have confirmed that internal bleeding from a damaged kidney due to HM exposure may result in the decreased generation of RBC (28). Pregnant women are a group whose biological indicators are highly important as disturbing the balance of metals in their body can harm both the mother and the infant (51). Lower blood concentrations of Cd in pregnant women have been associated with lower birth weight, a consistent risk factor for common chronic diseases and conditions. These results support that the spatial analysis of the blood concentrations of HMs can aid in focusing limited screening resources on smaller sub-populations with the highest risk of exposure. It was found that Cd, Pb, and As co-occurred in the blood of pregnant women, whereas women with elevated Hg concentrations were more likely to have lower Cd, Pb, and As (52). Plasma is a part of blood that is often neglected to applications. WBCs, RBCs, and platelets are essential for body function, but plasma also plays an important role that is not typically taken into account. Plasma transports all the components of the blood in the body. Accordingly, plasma is considered another fluid that can be employed to determine the concentration of metals. With exposure to the metals, some metals are eliminated by the body’s excretory mechanisms through sweat, urine, feces, and the like. In this respect, the level of exposure to the metals can be estimated by measuring them in the urine. Breast milk is the best food for a newborn. Human milk consists of 87% water, 1% protein, 4% lipid, and 7% carbohydrate (including 1-2.4% oligosaccharides). It also contains various minerals (Ca, phosphorus, magnesium, potassium, sodium, and the like) and vitamins (47). Therefore, mother’s milk is especially important between body fluids. The concentration of Pb has been indicated to be mostly higher than the concentration of Hg and Cd in the same cohort of breast milk. This is probably because, unlike Hg and Cd, Pb accumulates in the bones of mothers over a long period of time and is then released into the blood and breast milk along with Ca during pregnancy. Moreover, only an extremely small proportion of maternal Cd is released into the mothers’ breast milk because proteins that bind Cd in breast milk often bind more to Ca due to the high amount of Ca released into the
breast milk. Hence, there is a competitive inhibition of the binding proteins of Cd. Therefore, the amount of Cd in breast milk is influenced by a mother’s Ca level. Finally, the biochemistry of the interactions of these metals and proteins in breast milk is reasonably expected to vary and therefore will contribute to the inherent variation of these toxic metals in breast milk (53). Serum is a part of the blood that is similar in composition to plasma, but does not contain clotting factors. The components of plasma and serum are similar because they both contain hormones, glucose, electrolytes, antibodies, antigens, nutrients, and some special particles, except for clotting factors that are only present in plasma. Blood serum is one of the body fluids that can be used to measure the concentration of metals. Saliva is a clear liquid that is secreted by salivary glands. This liquid is one of the most important factors that facilitates swallowing and tasting. Most of the saliva is made up of water. For this reason, one of the ways to detect exposure to foreign substances such as metals is to measure them in the saliva.

**Conclusion**

Some of the metals in the body do not have a toxic effect on certain concentrations and even help improve the functioning of the body system. Smoking, which is widely common among young people today, is one of the factors that disturbs the balance of the concentration of these metals in the body. Smoking causes a significant increase in HMs in body fluids and even decreases essential metals such as Fe. People exposed to tobacco smoke, especially children, are affected by the disturbance of the balance of metal concentrations in the body. In addition, pregnant women who are E-ETS or smoker mothers are affected, and even the concentration of metals in their milk will change and can even significantly decrease the concentration of Fe in their milk.

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**Authors’ Contribution**

Conceptualization: Ali Momen, Roohollah Rostami.

Data curation: Ali Momen.

Formal analysis: Ali Momen.

Funding acquisition: Roohollah Rostami.

Investigation: Roohollah Rostami.

Methodology: Roohollah Rostami.

Project administration: Ali Momen.

Supervision: Roohollah Rostami.

Validation: Roohollah Rostami.

Visualization: Ali Momen.

Resources: Ali Momen, Roohollah Rostami.

Writing – original draft: Ali Momen.

Writing – review & editing: Roohollah Rostami.

**Competing Interests**

The authors certify that they have no affiliation with or financial interest in the subject matter or materials discussed in this research.

**Ethical Approval**

Not applicable.

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