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**Review Article**

# Exposure to Mercury in the Air and Its Effect on Cardiovascular Diseases (CVD): A Systematic Review

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**Abstract**

**Background:** We aimed to verify the exposure to mercury in the air and its effect on cardiovascular disorders.

**Methods:** The review was conducted using PubMed, Scopus, Web of Science, Embase, and national databases (such as SID) from 1995-2022.

**Results:** Mercury exposure can cause many disorders in humans, including neurodevelopmental disorders in fetuses and children, adverse cardiovascular outcomes, hypertension, and diabetes. Mercury is a human neurotoxin, and in recent years its potentially harmful effects on cardiovascular disease (CVD) have raised concerns, mainly due to mercury's role in reducing oxidative stress.

**Conclusion:** Possible mechanisms of mercury toxicity in CVD include mercury-selenium interaction, increased lipid peroxidation, and oxidative stress. In this article, we review studies that have investigated the relationship between mercury and CVD.

**Keywords:** Mercury; Cardiovascular disease; Exposure; Risk factors

## Introduction

Mercury is found in soil, water and air. Three forms of mercury in nature include: elemental, inorganic and organic mercury. All forms of mercury are toxic and dangerous to living things (1). Mercury is of human and natural origin. Human activities lead to environmental pollution with mercury. For example, the mercury level in surface water has increased significantly since the time of the Industrial Revolution. Mercury concentrations in Arctic marine animals have also increased by about 10 to 12 times (2). Mercury concentrations in the blood of seafood consumers are increasing worldwide. Global mercury emissions from natural and human resources are estimated at more than 6,000 tons per year (3). In particular, the share of human resources in mercury emissions is approximately 80% of annual emissions. Mercury levels in uncontaminated soil are approximately in the range of 10-50 µg/kg (2). However, values above 240 µg/kg were found in the mercury extraction region (4). The average total mercury gas in northern Europe, particulate mercury and reactive gas mercury are 1.98, 56 and 22 ng/m3, respectively. The concentration of mercury in the air can reach more than 190 ng/m3 in the mercury mine area (5).

The general population can be exposed to mineral mercury in a variety of ways, such as dental amalgam, inhalation of human resources such as metal extraction and smelting, combustion of fossil fuels, and incineration of municipal waste (6). The two main routes of exposure to methyl mercury for the general population are marine fish and freshwater consumption (7). Mercury exposure can cause many disorders in humans, including: neurodevelopmental disorders in fetuses and children, adverse cardiovascular outcomes, hypertension and diabetes (8).

One of the leading causes of death in the world is cardiovascular disease (CVDs). In high-income countries and some middle-income countries, the mortality rate due to cardiovascular disease has decreased, but it is still one of the most important causes of death in the world. In 2015, there were about 422.7 million and 17.9 million CVD cases and CVD deaths, respectively. The two main causes of CVD worldwide are ischemic heart disease and heart attack. Many factors contribute to CVD, including high blood pressure, high BMI, diabetes, consumption of salty foods, short-term or long-term exposure to air pollution, and hazardous chemicals in the air (such as heavy metals) (8).

We aimed to verify the exposure to mercury in the air and its effect on cardiovascular disorders.

## Materials and Methods

### *Search strategy*

The search strategy was carried out to obtain all articles on exposure to mercury in the air and its effect on cardiovascular diseases between 1995 and 2022. The review was conducted using PubMed, Scopus, Web of Science, Embase, and national databases (such as SID) (Table 1). The flowchart of the review article is available in Fig. 1.

The strategy was to use keywords search terms: Mercury, CVD, Source of Mercury, and Mercury exposure.

**Table 1:** Search terms and query results

| *Term* | *PubMed* | *Science Direct* | *Springer* | *Web of Science* | *Google Scholar* | *Unique results* |
|---|---|---|---|---|---|---|
| Air pollution | 20 | 30 | 23 | 23 | 52 | 148 |
| Mercury | 15 | 29 | 21 | 25 | 38 | 128 |
| carcinogenic | 19 | 28 | 12 | 18 | 16 | 93 |
| Cardiovascular disease | 18 | 20 | 18 | 19 | 48 | 123 |
| Total | 72 | 107 | 74 | 85 | 154 | 492 |

### *Study selection*

Evaluation of primary retrieval articles was done based on 1) title, 2) abstract and 3) full text of the articles.

Based on the title and abstract, some articles that were not about Risk factors and exposure to mercury and its effect on cardiovascular disease were removed. Related articles were downloaded after abstract screening.

Inclusion criteria: The screening criteria of the articles were: 1) Descriptive study on exposure to mercury 2) the full text is available 3) Unreview studies and 4) Mechanism of effect of mercury on cardiovascular disease.

Exclusion criteria: 1. The article is not in English, 2. The title is not relevant, 3. The abstract does not contain arsenic and liver cancer, 4. Repetitive articles, 5. Some information and data in the article is incomplete or limited, and as a result, they do not have priority to cite or extract, and 6. The study is non-experimental.

The obtained references were managed using EndNote X7 software.

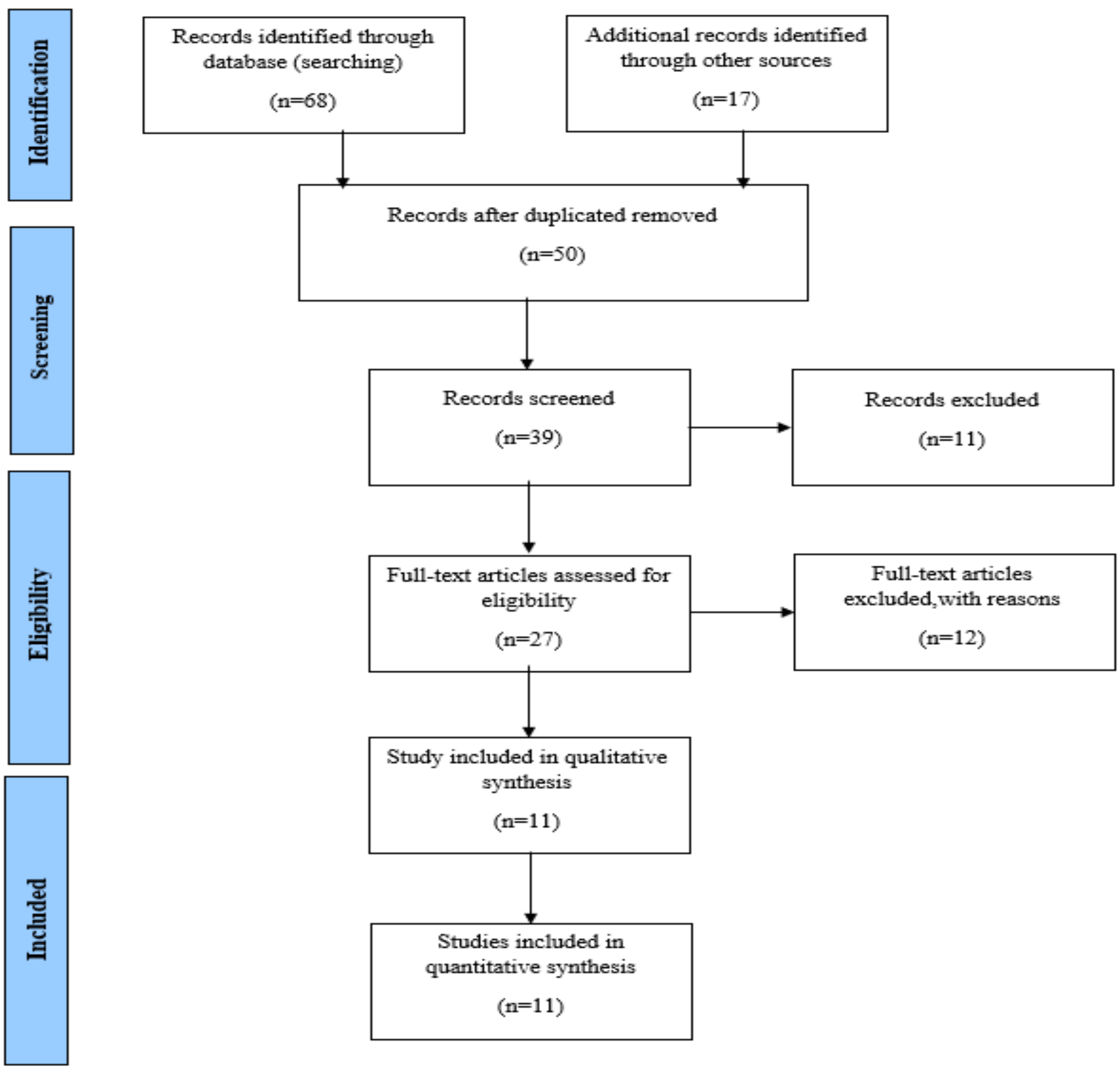


**Fig. 1:** Representation of the search strategy based on PRISMA flow diagram

## Results

### *The Chemical structure of Mercury*

Mercury is a heavy metal with an atomic number 80; Atomic weight 200.59; Density 13.59 g/cubic centimeter; Melting point -39 °C; boiling point 359 °C . This metal is extremely toxic and dangerous (9-11). This element is rarely found in the earth's crust, most of the time it exists in an inorganic form (such as mercury sulfide) (12). Mercury comes in two forms: inorganic mercury (such as mercury salts, and divalent mercury) and organic mercury (such as methyl mercury). The chemical structure of mercury causes different biological behaviors (13). Elemental mercury, or zero-valent mercury (Hg0), is a liquid at 25 °C that evaporates rapidly when heated above room temperature. The retention time of elemental mercury is one year in the atmosphere, where it can be transported and stored globally (14). Elemental mercury is easily oxidized in the atmosphere and turned into its inorganic forms (monovalent and divalent mercury) and is deposited in water and soil environments by rain. The respiratory system can easily absorb metal vapors, but they have a very weak absorption in the digestive system. Elemental mercury can reach target organs through cell membranes as well as cerebral and placental blood barriers. The solubility of elemental mercury plays a key role in this. The mineral forms of mercury, monovalent mercury, and divalent mercury do not have much ability to cross cell membranes because they are not lipophilic (15). The respiratory system can absorb inorganic mercury well through breathing, but it has little absorption through the skin and digestive system. The main routes of excretion of divalent mercury are through urine and feces. Its half-life is about two months (16, 17). Mineral mercury exists in different forms that have different uses, such as: 1. Inorganic mercury is used as an explosive detonator (such as ($Hg(CNO)_2$), 2. It can combine with chloride and create toxic and corrosive compounds (such as HgCl2) and 3. It can combine with sulfide and form as Pigment used in paints (such as HgS) (18). Inorganic mercury is converted to methyl mercury (MeHg) mainly by sulfate-reducing bacteria (19-21). Mineral mercury is absorbed through the gastrointestinal tract and is excreted mainly in the feces. Organic mercury, because it is lipophilic, can cross blood-brain and placental barriers, and through breast milk, infants can absorb these toxic compounds. Mineral mercury can accumulate in the liver, brain, kidneys, and muscles (19). Methyl mercury can accumulate in the body of organisms such as swordfish, sharks and marine mammals. Some marine fish can contain methyl mercury, which is 100,000 times greater than the surrounding aquatic environment (16).

### *Global Sources of Mercury Emissions in the Atmosphere*

Mercury in various meteorological layers comes from natural and human resources. Among the different meteorological layers, the contribution of the atmosphere to the global emission of mercury is much higher than the other layers, although large Mercury is deposited in the atmosphere on land and water (22, 23). Mercury produced in one place can be transported to another place during atmospheric transportation, depending on the direction and speed of the wind and the chemical properties of that element (24, 25). There are different forms of mercury in the atmosphere, which are expressed by special terms: THg (includes all forms of mercury), TGM (includes all gaseous forms of mercury), GEM (a form of elemental mercury that exists in a gaseous state), GOM (a form of oxidized mercury that exists in a gaseous state), RGM (a form of gaseous mercury that is highly reactive), TPM or Hgp (all mercury compounds found in suspended particles) and MeHg (an organic form of mercury) (26). The retention time of mercury or its derivatives in the air depends on many factors, the most important of which include weather conditions and the type of mercury in the air. For example, the retention time of gaseous elemental mercury (GEM) in the air is much longer than Total particulate mercury (TPM), so GEM can remain in the atmosphere for several months, while TPM remains in the atmosphere for a maximum of one day (because they quickly settle on the ground and are removed from the air) (27, 28).

### *Anthropogenic Emissions*

Mercury produced from human resources enters the environment mainly through industries, from where it is introduced as inorganic substances, wastes or a minor component in fuels (29). The main parameters affecting the amount of mercury emitted from human resources in industry depend on the level of mercury as a minor component in raw materials such as fuels, technology used in industrial processes, type and efficiency of equipment emission control (30). The United Nations Environment Program (UNEP) estimates that worldwide human mercury emissions in 2010 amounted to about 1960 tons per year (22). Artisanal and small-scale gold mining (ASGM) has been identified as a major source of anthropogenesis, accounting for 37% of total human mercury emissions into the global atmosphere. The use of fossil fuels in industries and residential places in order to use its energy and heat accounts for 25% of the total mercury emissions on earth (31, 32). There are other industrial sources that contribute to the global release of mercury into the atmosphere, including metal (non-ferrous) production (10%), cement production (9%), gold industry (5%), incineration (9%), manufacturing Ferrous metals (2.3%), chlorine industry (1.4%), fuel refineries (1.4%), and dental amalgam (0.2%) (30). Figure 2 shows the sources of anthropogenic mercury entering the air.

Wilson et al shows the total anthropogenic mercury emissions in the air in Table 2 (33).

**Table 2:** Global anthropogenic sources of mercury in the atmosphere

| ***Sector*** | ***Emission (Mg/kg)*** | | |
|---|---|---|---|
| | Average | Range | % |
| Coal combustion | 573.5 | 116.1-820.7 | 27.9 |
| Burning petroleum | 9.3 | 4.3-15.3 | 0.4 |
| Metallurgy (iron) | 45.4 | 16-88.4 | 2.2 |
| Metallurgy (Aluminum) | 5.9 | 2.1-11.6 | 0.3 |
| Metallurgy (Copper) | 20.3 | 7.2-39.2 | 1 |
| Metallurgy (Lead) | 32.4 | 11.6-62.7 | 1.6 |
| Metallurgy (Zinc) | 166.9 | 59.5-322.9 | 8.1 |
| Mercury production | 9 | 3.2-17.6 | 0.4 |
| Cement | 223.1 | 79.2-431.6 | 10.8 |
| Production of caustic soda and chlorine | 52 | 18.5-100.8 | 2.5 |
| Refineries | 49.9 | 23.1-82.4 | 2.4 |
| Gold production | 93.7 | 0.7-245.9 | 4.7 |
| ASGM | 659.4 | 409.7-906.2 | 32 |
| Incineration of waste—organized | 4.2 | 1.3-12.7 | 0.2 |
| Cremation | 4.8 | 1.4-14.3 | 0.2 |
| Other | 109 | 32.7-327.2 | 5.3 |
| All | 2063 | 1038-3499 | 100 |

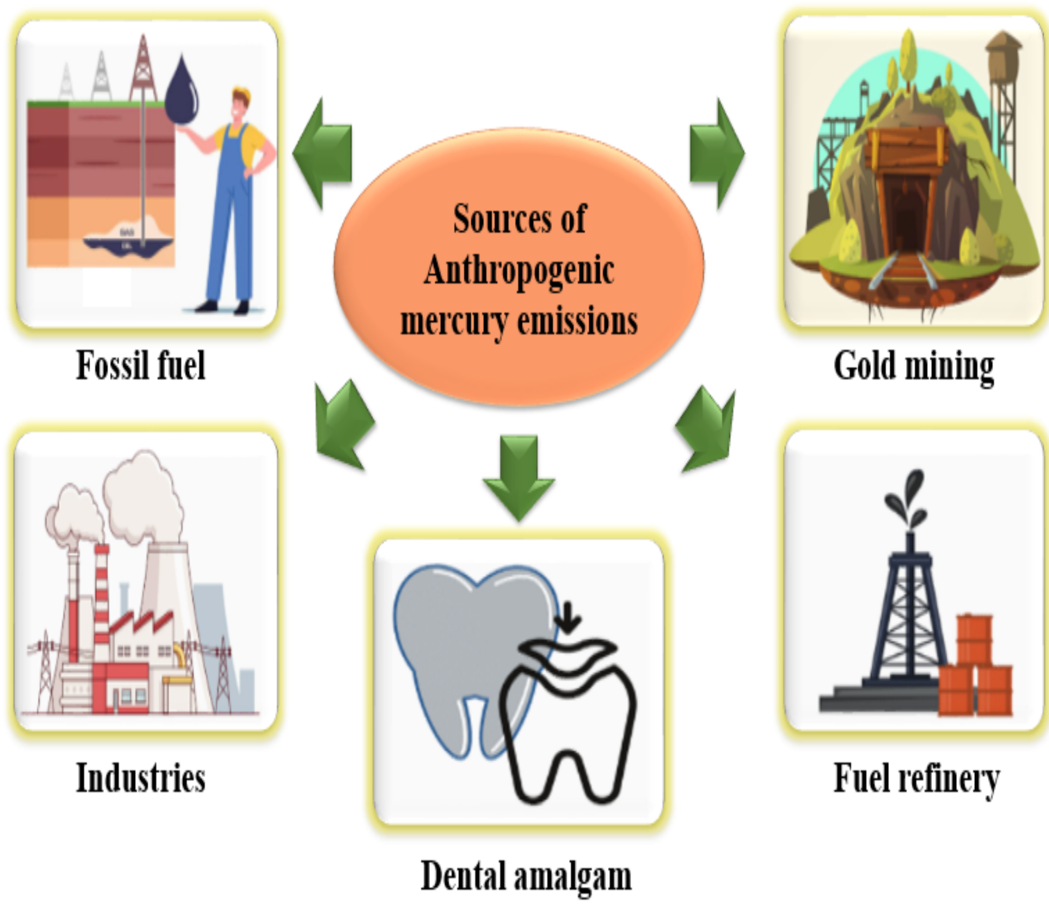


**Fig. 2:** Sources of anthropogenic mercury emissions (Originl)

### *Natural Emissions*

As a natural resource, mercury is produced in the earth's crust through the erosion of rocks and thermal activities of the earth's mantle (such as volcanic eruptions). Natural resources such as vegetation, land and surface water can also cause global mercury emissions (34). Mercury emitted from the surface of the oceans is in the form of Hg0, HgII and methyl (35). Mercury released from snow (north and south poles), unlike mercury released from plants, which is formed in the form of Hg0, is mostly oxidized and the amount of elemental Hg0 released is very low (1%). Meanwhile, there is mercury released from the soil surface to GEM, which depends on many factors, including: soil organic content, the amount and form of mercury in the soil, the angle of sunlight and, etc. Tropical forests and savannas play a very important role in releasing mercury into the atmosphere (36). Lands that contain a lot of peat can also release a lot of mercury into the air, so burning them contributes to the release of mercury into the atmosphere (37). The annual natural emissions of mercury vary from 3,600 tons per year to 5,300 tons per year (38). The GMOS project of the European Union estimated that primary emissions and re-emission processes from land surfaces and waters are the major contributors to mercury emissions to the atmosphere (5207 tons per year) (39). The project researchers found that as the primary natural source and redistribution, the oceans (36%) and biomass burning (9%) are the most important sources of mercury distribution worldwide. Forest areas (12%) and reeds and grasslands (9%). In general, the relative share of land and surface water is 2429 and 2778 tons per year, respectively, which leads to 5207 tons per year (40). Natural sources of mercury emissions are shown in Figure 3. Natural emissions of mercury can be divided into primary emissions (volcanic emissions) and secondary emissions. The results of Pirron et al.'s studies are shown in Table 3 (41). Table 4 lists several studies that have monitored mercury in the atmosphere.

**Table 3:** Mercury emission from natural sources and processes estimated for 2008

| *Source* | *Annual emission (Mg/year)* | *Relative Contribution (%)* |
|---|---|---|
| Oceans | 2682 | 50 |
| Lakes | 96 | 2 |
| Forests | 342 | 6 |
| Tundra/grassland/savannah/prairies/chaparral | 448 | 8 |
| Desert/ non vegetation zones | 546 | 10 |
| Contaminated sites (average between 138 and 263 Mg) | 200 | 4 |
| Agricultural areas | 128 | 2 |
| Evasion after mercury depletion events | 200 | 4 |
| Biomass burning | 675 | 12 |
| Volcanoes and geothermal areas | 90 | 2 |
| All | 5207 | 100 |

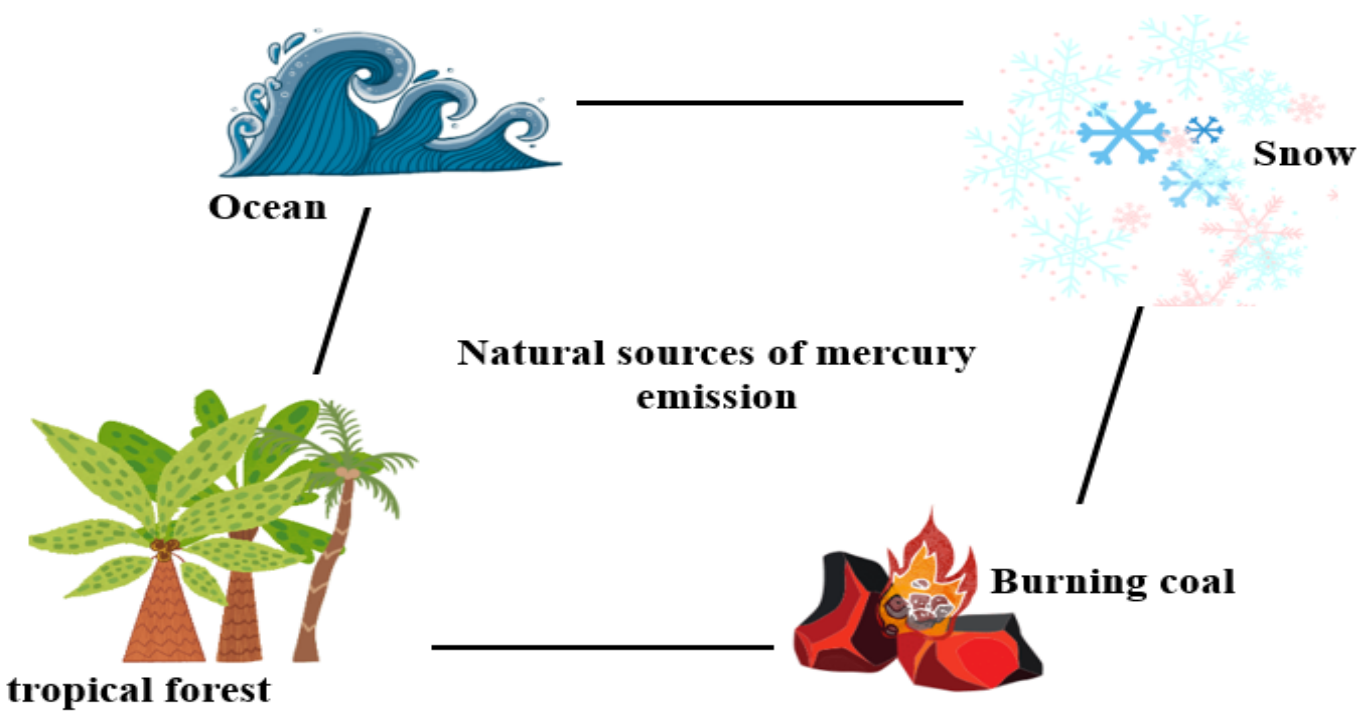


**Fig. 3:** Natural sources of mercury emission (Original)

**Table 4:** Monitoring mercury in the atmosphere

| *Authors* | *Country* | *location* | *Year* | *Type of mercury* | *Concentration (ng m⁻³ )* | *Measuring Tool* |
|---|---|---|---|---|---|---|
| Elaine Cairns et al. (42) | Canada (Toronto) | Urban area | 2009 | GEM | 1.89 ± 0.62 | Mercury Vapor Analyzer |
| Lee et al. (43) | England (Harwell) | Urban area | 1995 | TGM | 20.5 ± 1.5 | Mercury Vapor Analyzer |
| Benedetto et al. (44) | Mexico (Mexico City) | Urban area | 2020 | GEM | 30.23 | Portable Vapor Analyzer (Lumex RA 915 M) |
| WANG Zhang et al. (45) | China (Beijing) | Urban area | 2005 | $Hg^0$ | 6.5 ± 3.7 | Automated Mercury Analyzer RA-915+ |
| | China (Beijing) | | | | 13.5 ± 7.1 | |
| ShaofengWang et al. (46) | China (Guizot) | Lanmuchang Hg mining area | 2003 | TGM | 35.2 ± 26.1 | Dynamic Flux Chamber (DFC) |
| Ebinghaus et al. (47) | Irish (Mace Head) | Coast area | 2001 (6-year mean) | TGM | 1.75 | Automated Atomic Fluorescence (AFS) analyzer |
| Kock et al. (48) | Irish (Zingst) | Coast area | 2004 (6-year mean) | TGM | 1.64 | Cold Vapor Atomic Fluorescence Spectrophotometry (CVAFS) |
| Ewa Korejwo et al. (49) | Poland (Gdynia) | Coast area | 2017 | GEM | 1.7 | atomic absorption spectroscopy (DMA-80 mercury analyser) |
| W.angberg et al. (50) | - | Mediterranean region | 1999 | RGM | 1.6 - 2.4 | Mercury Vapor Analyzer (Tekrant 2537A) |
| Steffen et al. (51) | Canadian (Arctic) | snow area | 2000 | GEM | 3.25 | Mercury Vapor Analyzer (Tekrant 2537A) |
| Xuewu Fu et al. (52) | China (Tibetan plateau) | Mountain area | 2005 | TGM | 3.98 | Mercury Vapor Analyzer (Tekrant 2537A) |

## *Cardiovascular disease (CVD)*

The heart is the most important organ of the body for survival, whose task is to pump blood throughout the body. Delivering oxygen and nutrients to the organs and transferring carbon dioxide to the lungs (for its exit from the body by exhalation) is done by pumping blood. Every human heart can pump more than 7.5 cubic meters of blood daily (53). Cardiovascular disease is a type of disease that causes dysfunction of the heart and blood vessels. The term CVD includes cardiovascular diseases, such as coronary heart disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, and pulmonary embolism (54). Many factors play a role in causing this disease, including environmental factors (such as air pollution), genetic issues, nutrition, lifestyle change, social change, drug treatment and underlying diseases (high blood pressure, diabetes mellitus, obesity, and high blood cholesterol) (55). This disease is recognized as one of the most important causes of death worldwide, causing the death of 18 million people worldwide in 2015. Although this disease is increasing in developing countries, it has decreased significantly in developed countries. The average age of death due to cardiovascular diseases in developed countries is 80, but in developed countries it is 65 (56).

### *Heavy metals and health effects*

Heavy metals are necessary for the life of living organisms in small amounts, but if their amount increases in the body, they cause many problems. It is necessary to explain that each heavy metal has a target organ. Over time, they can be stored in that tissue and cause the destruction of that tissue or organ. Although all the health organizations in the world have declared that excessive exposure to heavy metals has adverse effects on humans, long-term exposure to them is still increasing in many parts of the world (57). The most common heavy metals in breathing air are arsenic, cadmium, lead, nickel and mercury, all of which pose risks to human health and the environment. By moving the main metals from their natural binding sites to protein sites, heavy metals cause cell dysfunction and ultimately toxicity. Oxidative deterioration of biological macromolecules is primarily due to the binding of heavy metals to DNA and nuclear proteins (58). Arsenic, lead, mercury, cadmium and chromium by affecting the sulfhydryl group of cells, proteins, nucleic acid, membranes, lipids, as well as binding with cysteine, glutamate and histidine ligands cause disruption in cellular respiration, cellular enzymes and mitosis (59).

### *Mercury as a risk factor for cardiovascular diseases*

Heart diseases are one of the most important diseases in the world. Despite significant advances in the treatment of CVD, there are approximately one million deaths per year in the United States. About 82% of deaths in developing countries are related to CVD (60). WHO stated that the death rate is closely related to many factors, including the age and income of people, so that in developed and industrialized countries, the death rate due to cardiovascular disease is much lower than in low-income countries. This organization also stated that as people age, the possibility of suffering from heart disease will increase. (61). In 2015, when there were more than 400 million deaths and 18 million deaths from CVD, the share of deaths in high-income countries from cardiovascular disease had declined. The researchers said that the annual death rate of CVD will reach 23.6 million by 2030 (62). Cardiovascular diseases are affected by environmental factors, diet and lifestyle. They are of great public health importance (63). The effects of confounding variables are complex, including potential mediators and moderators (risk modifiers). These complex pathways include individual characteristics (e.g., age, gender, race/ethnicity), socioeconomic status, behavioral habits (e.g., dietary habits); Dose of heavy metals; Health condition (64). Ischemic heart disease (IHD) and stroke are two key factors in the development of CVD. There are various diseases in all countries of the world, but cardiovascular disease is very common in Asian countries, so that it was the most important cause of death in 2019. 35% of all deaths in Asia (10.8 million deaths) were due to cardiovascular disease. More than 35% of these CVD deaths were untimely (Death of people under 70 yr old). Premature deaths were much higher than premature deaths from heart disease in the United States (24%), Europe (21%) and worldwide (35%) (65). The most common causes of CVD in Asia include IHD and stroke, the epidemics of which vary considerably between regions and countries in Asia. In Central Asia (62%), West (60%) and South (57%), IHD It is more prevalent, but stroke was the most common cause of death from cardiovascular disease in East and Southeast Asia (66). The death rate due to ischemic heart disease is significantly different from the death rate due to heart attack in some Asian countries. For example, the death rate due to ischemic heart disease in Lebanon and Uzbekistan is much higher than the death rate due to heart attack. However, in the countries of

Vietnam and Myanmar, the death rate due to heart attack is higher than ischemic (67, 68).

### *Mechanism of effect of mercury on cardiovascular disease*

Mercury simultaneously binds to molecules containing thiol (-SH) and selenium, which finally form selenium-mercury complexes. On the other hand, the level of selenium has a direct relationship with the activities of enzymes, so that a decrease in selenium causes a decrease in the activity of superoxide dismutase and catalase (69). In addition, one of the body's defenses against mercury is binding to glutathione, which can reduce cellular defenses against oxidation. Mercury is likely to be excreted from the body through glutathione-mercury complexes (70). Increased reactive oxygen species (ROS) and decreased activity of dangerous antioxidant enzymes are two important risk factors for cardiovascular disease. In addition, mercury plays a key role in enhancing LDL oxidation and can disrupt the phospholipid integrity of plasma membranes through foreign phosphatidylserine (71). Inactivation of paraoxonase, an extracellular antioxidant enzyme that causes HDL inefficiency, is another mechanism that causes the deleterious effects of mercury on cardiac disorders. This enzyme is also very important as an LDL antioxidant and can cause atherosclerosis (72). Even in animals, mercury can cause several inflammatory diseases in the heart (73). Mercury plays a key role in causing cardiovascular problems by producing arachidonic acid metabolites that can cause an inflammatory reaction (74). According to Salonen et al.'s research, increased levels of mercury in hair and excessive consumption of fish (contaminated with mercury) increase the risk of heart attack. (75).

Mercury-induced oxidative stress can damage myocardial tissue, as evidenced by epidemiological studies. Mercury can have a deleterious effect on the heart by inducing oxidative stress, reducing sulfhydryl groups, and altering mitochondrial function (76). Antioxidants are a good protector of the body's immunity against the toxicity caused by methylmercury. However, mercury can reduce the antioxidant defense capacity by disrupting the redox balance (77). The mechanism of mercury's effect on cardiovascular diseases is shown in Fig. 4.

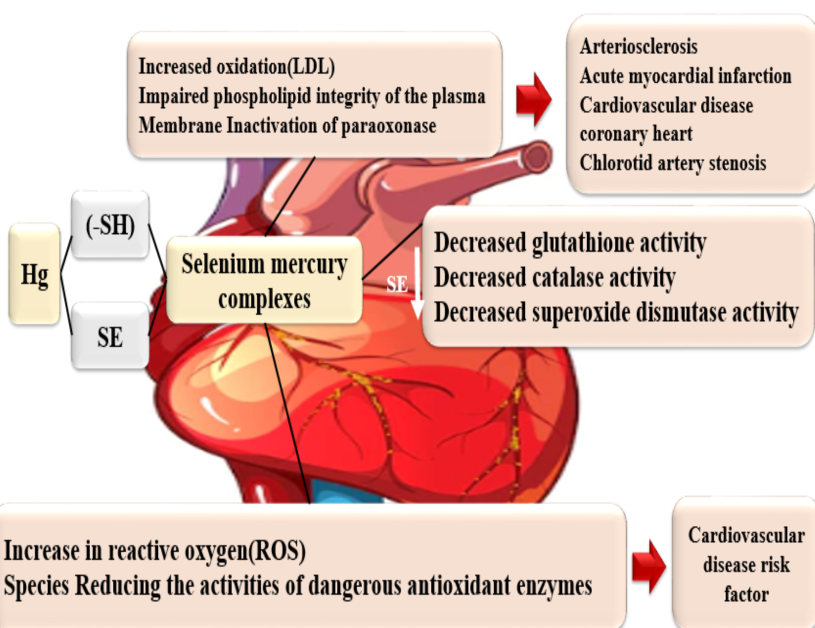


**Fig. 4:** Mechanism of effect of mercury on cardiovascular disease (Original)

How much methylmercury intake can be consumed so that the blood level does not exceed the standard level? The EPA defined RFD as a daily exposure to the human population that is likely to have no adverse effects throughout life (EPA, 2002). The RFD principle for safe exposure to hazardous substances has been accepted in epidemiological studies. EPA stated that the RfD for methylmercury is 0.1 μg/kg.day (78).

One of the limitations of the present study is the lack of examination of various aspects of disorders caused by exposure to mercury.

## Conclusion

Mercury comes in three forms: inorganic mercury (such as liquid metal mercury and mercury vapor, mercury salts, and divalent mercury) and organic mercury (such as methyl mercury, ethyl mercury, and phenyl mercury). The chemical structure of mercury causes different biological behaviors. Most of the human and health risks associated with mercury are due to the use of dental amalgam, the use of cosmetics, exposure to ASGM, the consumption of rice, seafood such as fish and fresh water. Cardiovascular diseases are affected by environmental factors, diet and lifestyle. They are of great public health importance. Possible mechanisms of mercury toxicity in CVD include: Mercury–selenium interaction, Promotion of lipid peroxidation and oxidative stress.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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