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Effects of cadmium toxicity due to air pollution in industrial countries on animal fetal respiratory system development; current knowledge and future directions

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ABSTRACT

Cadmium (Cd) exposure, particularly from atmospheric pollution in industrialized countries, presents considerable hazards to the development of the fetal respiratory system. This study examines the existing literature on cadmium toxicity, highlighting its harmful effects on lung development as observed in animal studies. Evidence suggests that maternal cadmium exposure, facilitated through methods such as intraperitoneal injection in rodent models, results in adverse consequences for offspring, including modifications in gene expression and compromised lung structure and functionality. Cadmium is primarily absorbed via the respiratory system, with inhalation associated with a range of respiratory ailments, including chronic lung diseases and lung cancer. Additionally, cadmium exposure has been linked to complications during pregnancy, such as miscarriage and low birth weight, likely due to mechanisms involving endocrine disruption and oxidative stress. This study underscores the necessity of comprehending cadmium's impact on fetal development and the potential protective effects of nutrients during gestation. Given the strong association between cadmium exposure and adverse health effects, further investigation is warranted to clarify these impacts' underlying mechanisms and identify preventive measures. This paper offers a thorough overview of cadmium's influence on the development of the fetal respiratory system and proposes future research directions in this vital area of public health.

Keywords: Cadmium, Respiratory system, Fetus.
Article type: Review Article.

INTRODUCTION

Cadmium (Cd) is classified as a malleable metallic element displaying in the form of a bluish or silvery-white powdered substance. This element exhibits a propensity to readily engage in chemical reactions with a variety of compounds that are prevalently utilized within electrochemical cells and batteries, encompassing nickel-cadmium

batteries, various alloys, pigments, plastic stabilizers, dyes, paints, as well as applications in glass manufacturing and the galvanic sector. The element was first identified by F. Stromeyer in 1817 in Göttingen, Germany (Homburg 1999). Cadmium plays a critical role in nuclear reactors, functioning as a moderator for the uranium fission process via mechanisms of electron capture. It is found in its natural state within soil, mineral deposits (including sulfides, sulfates, carbonates, chlorides, and hydroxide salts), and aquatic environments. Cadmium is typically extracted as a secondary product from zinc sulfide (ZnS) during zinc production. However, due to its analogous physicochemical characteristics, it is often encountered with zinc, lead, or copper (Himeno *et al.* 2019). The highest levels of cadmium exposure are predominantly associated with activities in the metallurgical sector. Over the past century, numerous pathways for cadmium exposure have been delineated, with its environmental presence being a direct result of diverse anthropogenic interventions. The enduring sources of cadmium contamination are linked with its deployment in industrial applications as a corrosive agent and its use as a stabilizing compound in polyvinyl chloride (PVC) materials, colorants, and nickel-cadmium batteries. Household dust is a potential cadmium exposure conduit in locales characterized by soil contamination. The anthropogenic inputs of cadmium into the environment stem from the smelting and refining processes of copper and nickel, fossil fuel combustion, and phosphate-based fertilizers (Järup 2002; Genchi *et al.* 2020). Furthermore, cadmium is acknowledged as a contaminant arising from non-ferrous metal smelting activities and electronic waste recycling. Natural occurrences such as volcanic eruptions, the gradual weathering of geological formations and soil through erosive processes, and forest fires also contribute to the elevation of cadmium concentrations in various environmental compartments (including the atmosphere, soil, and water). Moreover, the operations associated with zinc, lead, and copper mining exacerbate the atmospheric release of this metal, consequently resulting in soil contamination. The absorption of cadmium predominantly transpires through the respiratory tract, with a lesser extent of absorption occurring via the gastrointestinal pathway, while dermal absorption remains comparatively rare. Once internalized, erythrocytes and albumin convey cadmium into the bloodstream, accumulating within the kidneys, liver, and gastrointestinal system (Genchi *et al.* 2020). The process of cadmium elimination from the human body is notably prolonged, occurring chiefly through renal excretion, as well as in urine, saliva, and through lactation in breast milk. In humans, exposure to cadmium has been associated with a range of deleterious health outcomes, encompassing renal and hepatic dysfunction, pulmonary edema, testicular damage, osteomalacia, and impairment of the adrenal glands and hematopoietic system. A significant correlation has also been established between biomarkers indicative of cadmium exposure (detected in blood and urine samples) and various medical conditions, including coronary heart disease, stroke, peripheral arterial disease, and atherogenic modifications in lipid profiles (Satarug 2018). The primary objective of the investigation into cadmium (Cd) toxicity is to examine the repercussions of cadmium exposure on the development of the fetal respiratory system, especially within the framework of air pollution prevalent in industrialized nations. This research intends to clarify how cadmium, a hazardous metal commonly found in industrial settings, impacts the development of fetal lungs and overall respiratory health. It will investigate the pathways through which cadmium exposure can result in adverse health outcomes for offspring, including developmental anomalies and compromised lung function. The study will also delve into the consequences of maternal cadmium exposure during gestation, evaluating its potential effects on fetal health and its role in the emergence of long-term respiratory problems in children. It underscores the significance of understanding how cadmium can be transferred across the placenta and its capacity to inflict damage before birth.

Cadmium

Cadmium (Cd; atomic number 48, atomic weight 112.41) is classified within group XII of the periodic table of elements. This soft, silvery-white metal exhibits chemical resemblances to zinc and mercury, reflected in its physical and chemical characteristics. The atomic weight of cadmium arises from the presence of eight stable isotopes. It is categorized as a post-transition metal, characterized by two electrons in its s orbital and a fully occupied d orbital. Furthermore, cadmium is soft, malleable, and ductile like zinc, typically adopting a +2 oxidation state in most of its compounds. Cd demonstrates corrosion resistance, rendering it suitable for application as a protective coating; it is insoluble in water and non-combustible. Upon combustion in air, cadmium yields cadmium oxide. Cadmium dissolves in hydrochloric, sulfuric, and nitric acids, producing correspondingly cadmium chloride, cadmium sulfate, and cadmium nitrate. Additionally, cadmium finds utility in control rods for nuclear reactors, serving as a neutron absorbent to regulate neutron flux during nuclear fission (Genchi *et al.* 2020).

Cadmium sources

The primary origin of cadmium is stack dust, produced during the distillation process of zinc refinement. Due to its significant volatility, this substance is dispersed across all fractions. Cadmium is predominantly used to coat various metals, with steel being the principal target, or as an anticorrosive layer on steel sheets. It serves as an exceptionally effective protective coating in alkaline environments and is frequently employed in the manufacture of low-melting alloys, such as Wood's metal, which is utilized in fire extinguishing systems. Presently, heavy industries in Poland are nearly vanishing, consequently making the primary pathways of cadmium exposure within the nation cigarette smoking and consuming contaminated food. Moreover, Tchounwou *et al.* identified similar avenues of cadmium exposure in the United States. Beyond the consumption of tainted food and smoking, individuals may encounter cadmium through various means, including employment in the metallurgy sector or working at sites contaminated with cadmium (Tchounwou *et al.* 2003).

Exposure to Cadmium and Toxicity

Cadmium, recognized as a detrimental environmental contaminant, has been introduced into ecosystems primarily due to rapid industrial growth and modern technological practices. This metal is absorbed in considerable quantities through polluted water, food, and air. Notably, high cadmium concentrations exist in marine species, including crustaceans, bivalve mollusks, oysters, cephalopods, and crabs. It is also found in organ meats such as liver and kidneys, as well as in oilseeds, cocoa beans, and certain wild mushrooms (Sirot *et al.* 2008; Satarug 2018). Generally, plant-based foods tend to have higher cadmium levels compared to animal products like meat, eggs, milk, and dairy, depending on the extent of soil contamination. Staple crops, particularly rice and wheat, along with green leafy vegetables, potatoes, carrots, and celery, may contain elevated cadmium concentrations relative to other plant foods (Fig. 1). As a result, individuals following vegetarian diets or consuming shellfish may face increased cadmium exposure compared to those with omnivorous diets. A significant route of human cadmium exposure is through rice consumption. Consequently, the practice of flooding rice paddies during harvest is recommended as a water management strategy to reduce cadmium accumulation in rice, especially in areas of Japan with high soil contamination. However, this technique may inadvertently lead to increased arsenic levels in the rice. Cadmium exhibits unique hydrochemical characteristics that enhance its mobility within groundwater systems. At near-neutral pH levels (below 6.5), cadmium remains dissolved, contrasting with the typical behavior of other heavy metals that tend to adhere to soil particles. Thus, the contamination of drinking water and river systems with cadmium is a significant concern, particularly near industrial or mining sites. Furthermore, tobacco use constitutes another primary source of cadmium exposure for the general population, with the levels of cadmium inhaled from cigarette smoke varying according to the type of tobacco product (Taha *et al.* 2018).

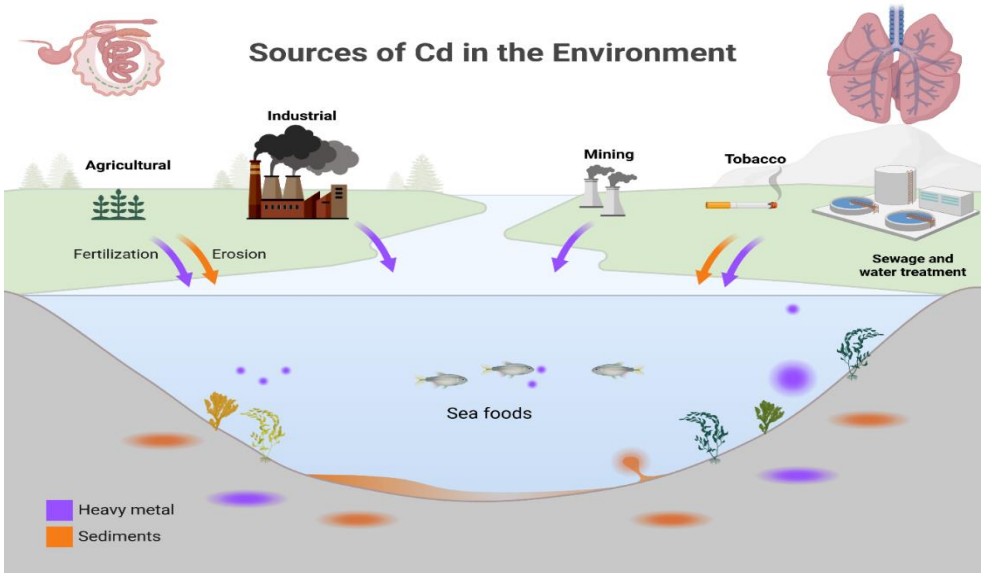

Fig. 1. Various sources of cadmium in the environment include industrial factories, agriculture, mining, tobacco, water contamination.

Cigarettes typically contain about 1-2 µg cadmium (Cd), meaning that an individual who smokes 20 cigarettes per day would likely absorb approximately 1 µg of this heavy metal. Around 10% of inhaled cadmium is estimated

to be absorbed, with an efficiency ranging from 40% to 50% within the respiratory system. The inhalation of cadmium has been linked to a variety of respiratory disorders associated with smoking, including chronic pulmonary diseases and lung cancer. Research conducted by Mona *et al.* indicated a significant increase in cadmium levels in the serum and urine of smokers compared to non-smokers. Furthermore, they found a marked rise in the incidence of bone pain among smokers, with rates of 95% in smokers versus 37.7% in non-smokers. The authors concluded that long-term exposure to cadmium may have osteotoxic effects, contributing to the deterioration of bone tissue (Tchounwou *et al.* 2003). Cadmium accumulates in plants and animals with a long half-life of about 25–30 years. Epidemiological data suggest that occupational and environmental cadmium exposures may be related to various types of cancer and diseases of the organs, such as lung, nasopharynx, pancreas, gastrointestinal, liver, brain, and kidney (Fig. 2).

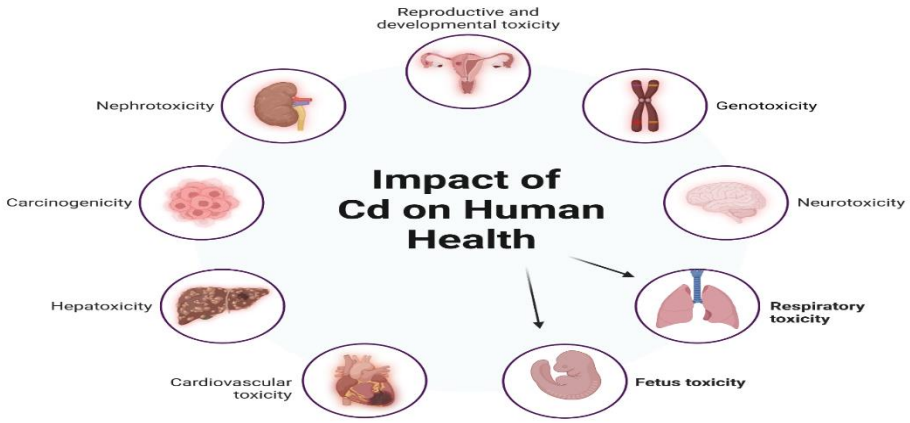

Fig. 2. Effect of Cd accumulation in various organs in the animal and human body.

Pathological Consequences in the Respiratory System

Cadmium (Cd) exposure within the respiratory system can irritate the nasal mucous membranes, impairing the sense of smell and affecting the upper respiratory tract. Occupational poisoning, particularly prevalent in the metallurgical industry, is primarily caused by inhaling fumes generated during the welding, melting, or soldering materials containing cadmium. Evaluations of respiratory health can be conducted through laryngological assessments, spirometry, and chest X-rays. The initial symptoms of cadmium poisoning often mimic those of metallic fever and pulmonary edema, potentially manifesting within 24 hours of exposure. Acute toxicity is associated with fume concentrations of 0.5 mg m^{-3} and a respirable dust level of 3 mg m^{-3}. This condition frequently leads to chronic bronchitis, with workers in the metallurgical sector commonly experiencing reduced olfactory function (or complete anosmia), nasal mucosa dryness, or ulcerative lesions. A dry cough is typically the first symptom, which may evolve into expectoration consistent with chronic bronchitis. Emphysematous changes linked to cadmium exposure are characterized by exertional dyspnea, decreased physical stamina, and reduced pulmonary ventilation efficiency. Long-term inhalation of cadmium particles is associated with the lung function abnormalities and chest radiographs that suggest emphysema, while exposure to airborne cadmium is correlated with compromised olfactory capabilities (Charkiewicz *et al.* 2023).

Cd consequences in the fetal respiratory system

The most significant complication during early pregnancy is spontaneous abortion, which poses a considerable challenge to reproductive health. This phenomenon can arise from many factors, including cytogenetic, immunological, and endocrinological influences. Additionally, the impact of environmental toxins should not be underestimated, as such toxicity may adversely affect ovarian function within the female reproductive system. Cadmium, classified as a non-essential metal, represents a considerable risk to food safety and public health. This threat is especially critical for infants and young children, who have a higher food intake relative to their body weight and possess developing physiological systems. This review investigates the health hazards linked to Cd exposure, focusing on the period from prenatal development through adolescence. It assesses the prevalence of Cd-laden foods in children's diets and their consumption levels across different nations (Chunhabundit 2016). The findings indicate a correlation between Cd exposure and various health issues, including neurodevelopmental

disorders, immune system impairments, and cardiovascular diseases. Furthermore, the review provided by Huang *et al.* underscores regional disparities in exposure, noting that certain Asian countries, such as Thailand and China, report elevated levels of Cd intake among children compared to other areas. To address the issue of Cd exposure in early childhood, the review proposes several strategies, including reducing Cd levels in food, preventing its absorption, and enhancing its elimination from the body. To effectively lower the risk of dietary Cd intake in children, it is essential to enforce strict regulations on Cd limits in food products for children, supported by a collaborative effort among multiple stakeholders. This review offers valuable insights for formulating public health policies and contributing to achieving broader public health objectives (Huang *et al.* 2024). The presence of heavy metals in the environment, along with human exposure through air and cigarette smoke, has contributed to a global rise in respiratory diseases. While the impact of oral exposure to heavy metals on liver and kidney structure and function has been extensively studied, the respiratory system often remains underexplored (Mitra *et al.* 2022). An experimental study aimed to examine potential structural alterations in the lung tissue of Sprague-Dawley rats following 28 days of oral exposure to cadmium and mercury (Hg), both individually and in combination, at concentrations 1000 times higher than the World Health Organization's recommended limits for these metals in drinking water. Post-exposure assessments involved histological techniques and transmission electron microscopy (TEM) to evaluate the overall morphology of the bronchioles and lungs and the distribution of collagen and elastin. Observations revealed structural modifications in the alveoli, including collapsed alveolar spaces, infiltration of inflammatory cells, and thickening of the alveolar walls. Furthermore, exposure to Cd and Hg led to degeneration of alveolar structures, resulting in confluent alveoli. Changes in bronchiole morphology were characterized by an increase in smooth muscle mass, along with degeneration, detachment, and aggregation of the luminal epithelium. Notably, the group exposed to Cd and Hg exhibited pronounced bronchiole-associated lymphoid tissue. Ultrastructural analysis revealed fibrosis, with the Cd-exposed group showing a dense arrangement of collagen fibrils, while the Hg-exposed group showed a notable elastin increase. This research highlights the lungs as a target for heavy metal toxicity following oral exposure, leading to cellular damage, inflammation, and fibrosis, thereby elevating the risk of respiratory diseases, with Hg demonstrating the most significant fibrotic impact, particularly when combined with Cd (Koopsamy Naidoo *et al.* 2019). Cadmium exposure, even at low levels, can result in significant harm to various organ systems, including the kidneys, liver, skeletal system, and cardiovascular system, as well as impairments in vision and hearing. In addition to its pronounced teratogenic and mutagenic properties, cadmium has been shown to exert detrimental effects on human reproductive health for both males and females, influencing pregnancy outcomes. These adverse effects are attributed to alterations in gene expression within the embryo, which lead to abnormal methylation patterns in both the placenta and the embryo. The epigenetic modifications associated with cadmium exposure are thought to arise from its propensity to bind to thiols, which results in a depletion of the methyl donor S-adenosyl methionine. This depletion can lead to changes in the methylome and subsequently affect the activity of DNA methyltransferases, potentially resulting in disorders related to placental and fetal development (Geng & Wang 2019). Elevated levels of cadmium in the placenta are associated with heightened expression of the metallothionein gene family. Metallothionein, a protein rich in cysteine, acts as a protective mechanism, inhibiting the passage of toxic metals through the placenta. Cadmium has the potential to displace zinc in the developing fetus, a trace element essential for normal growth and development. To safeguard the fetus, metallothionein sequesters cadmium. However, this process simultaneously diminishes the bioavailability of zinc, which is critical for cellular division and differentiation. Notably, infants with low birth weight exhibit significantly elevated cadmium levels alongside reduced zinc concentrations (Pabis *et al.* 2021). Furthermore, cadmium exposure can lead to decreased leptin hormone synthesis, increased corticosterone levels, and disruption of progesterone production within the placenta. Recent studies included in this meta-analysis reveal a marked difference in blood cadmium levels between affected and unaffected groups, suggesting that recent exposure to cadmium may be more closely linked to embryotoxicity and spontaneous abortions than the overall cadmium burden in the body. Approximately one-third of all conceptions and 10–15% of clinically confirmed pregnancies result in pregnancy loss or miscarriage. Cadmium's influence on pregnancy loss may occur through endocrine mechanisms or by exacerbating oxidative stress, which has been associated with adverse reproductive health outcomes. In a study examining blood cadmium levels, control females—those without a documented history of pregnancy loss exhibited a mean concentration of 0.25 μg L^{-1}. In contrast, females who reported experiencing recurrent pregnancy losses, defined as three or more instances, had a mean blood cadmium level of 0.46 μg L^{-1}. To elucidate the

potential association between cadmium exposure and pregnancy loss, further prospective research is necessary, particularly at levels of cadmium exposure that are relevant to environmental conditions, due to a significant lack of human data on this topic (Ali *et al.* 2023). Cadmium toxicity resulting from atmospheric contamination in industrialized nations presents considerable hazards to the ontogeny of the fetal respiratory system in various animal models. Prenatal exposure to Cd can significantly disrupt pulmonary development, culminating in enduring health complications. This concern is particularly pronounced in industrialized locales where Cd is ubiquitous due to various anthropogenic activities. The extant comprehension of Cd influence on fetal respiratory maturation is predicated on multiple investigations that underscore its deleterious effects on cellular and molecular strata. Prospective avenues for research encompass the exploration of mitigation strategies and the elucidation of the specific mechanisms underlying Cd-induced toxicity (Young & Cai 2020). Yong-Wei Xiong *et al*. developed a mice model to investigate the impact of maternal cadmium exposure at various gestational stages on fetal development and the biosynthesis of progesterone in the placenta. Pregnant mice were assigned to four distinct groups. The Cd groups received cadmium chloride ($CdCl_2$) at a concentration of 150 mg L^{-1} through their drinking water during early (days 0-6), middle (days 7-12), and late (days 13-17) gestation periods, respectively. The control group was provided with reverse osmosis (RO) water. Findings indicated that maternal exposure to cadmium during the late gestation period significantly reduced both fetal weight and length. Notably, the placental cadmium concentration was highest during this late exposure phase compared to the earlier stages. Furthermore, late gestational exposure to cadmium significantly decreased progesterone levels in both maternal serum and the placenta. Correspondingly, the expression of critical progesterone synthesizing enzymes, such as steroidogenic acute regulatory protein (StAR) and 3β-hydroxysteroid dehydrogenase (3β-HSD), was markedly downregulated in the placenta of mice exposed to cadmium during late gestation. These results suggest that maternal cadmium exposure during the late stages of pregnancy, rather than during early or middle stages, contributes to fetal growth restriction, potentially through the inhibition of placental progesterone synthesis (Xiong *et al.* 2020). Prenatal exposure to Cd interferes with nascent airway development by influencing cellular proliferation and differentiation. This is substantiated by alterations in gene expression and chromatin accessibility within embryonic pulmonary cells, particularly affecting *Sox2+* and *Wnt2+* progenitor populations. Cd exposure in gestating animals is associated with heightened expression of genes such as P53, which correlates with lung tissue damage and inflammatory responses in neonates. Cd is capable of traversing the placental barrier, precipitating potential developmental impairments and respiratory complications in progeny, as evidenced by both human and animal investigations. Nutritional supplements, including Vitamin D and Magnesium, have demonstrated potential in mitigating Cd-induced pulmonary toxicity. These supplements are instrumental in modulating inflammatory responses and enhancing lung architecture in neonates. Environmental regulatory measures, such as reducing Cd emissions from industrial operations, are imperative for minimizing exposure and associated health risks (Li *et al.* 2023). Further investigations are essential to clarify the mechanisms underpinning Cd-induced toxicity at environmentally pertinent doses, emphasizing long-term health ramifications. Developing novel therapeutic interventions to counter Cd toxicity and promote fetal lung development is paramount. While the prevailing research furnishes valuable insights into the ramifications of Cd on fetal respiratory maturation, there exists a necessity for more exhaustive studies to discern the long-term consequences comprehensively and to formulate effective mitigation strategies. Moreover, the influence of additional environmental pollutants in conjunction with Cd exposure merits further scrutiny to evaluate their collective impact on fetal health. The Rutter *et al.* research underscores the compromised functionality of vital regulatory genes, Gata6 and Gli2, pivotal to the noted disturbances in lung development. Additionally, it reveals metabolomic alterations in pathways associated with polyamine, tyrosine, and fatty acid biosynthesis, suggesting a complex influence of heavy metal exposure on cellular and molecular mechanisms during a crucial phase of lung development (Rutter *et al.* 2010). The research by Amanpour *et al.* involved the administration of cadmium at a dosage of 2 mg kg^{-1} body weight via intraperitoneal injection to female rats for 28 days before mating. Subsequently, the pregnant rats were categorized into groups that received either phosphate-buffered saline (PBS), vitamin D, magnesium, or a combination of vitamin D and magnesium. The research indicates that maternal exposure to cadmium has a significant detrimental effect on the lung development of newborns, as demonstrated by an increase in P53 gene expression and a decrease in *Foxo1* gene expression, both of which adversely influence lung structure and function. These results underscore the harmful effects of environmental toxins on the development of fetal lungs. Furthermore, supplementing vitamin D and magnesium (Mg) during pregnancy appears to counteract the negative

consequences of Cd exposure. These nutrients contribute to reducing inflammation, promoting the expression of protective proteins such as VEGF and BMP-4, and enhancing the overall pulmonary health of newborns, thereby suggesting a viable therapeutic strategy for alleviating Cd-related lung toxicity (Amanpour *et al.* 2024). The article released by Lalit in 2021 examined the evidence suggesting that exposure to cadmium during pregnancy and early childhood is linked to significant health complications, including developmental disorders, reduced birth weight, and cognitive impairments in children. It underscores the ability of cadmium to traverse the placental barrier, which may result in long-term detrimental health effects that can emerge both in infancy and later in life. The results indicated a relationship between increased cadmium concentrations in maternal and umbilical cord blood and adverse pregnancy outcomes, such as smaller head circumference at birth and hindered growth in children up to three (Chandravanshi *et al.* 2021). Cadmium exposure is recognized as a developmental toxicant in animal studies, resulting in fetal malformations and various negative outcomes. Nevertheless, definitive evidence concerning its effects on the development of the human fetal respiratory system remains lacking. Existing research suggests that inhalation of cadmium can induce pulmonary irritation, and prolonged exposure may contribute to kidney disease. However, the specific implications of cadmium on fetal respiratory development, particularly concerning air pollution in industrialized nations, necessitate additional investigation to clarify the connections and underlying mechanisms involved. Cadmium exposure is associated with a range of health complications, particularly respiratory disorders resulting from inhalation. Acute exposure primarily leads to pulmonary irritation, while chronic exposure is linked to renal disease due to the accumulation of cadmium in the kidneys. Furthermore, there is a noted correlation between cadmium exposure and an elevated risk of lung cancer; however, the findings from human studies remain inconclusive due to various confounding variables. The research indicated that the Environmental Protection Agency (EPA) categorizes cadmium as a Group B1 probable human carcinogen. Although studies conducted on animals have demonstrated an increased incidence of lung cancer following prolonged inhalation exposure, definitive evidence regarding its carcinogenic potential in humans is still absent (Haney 2016).

CONCLUSION

Cadmium exposure, particularly from atmospheric pollution in industrialized countries, presents considerable hazards to the development of the fetal respiratory system. This paper examines the existing literature on cadmium toxicity, highlighting its harmful effects on lung development as observed in animal studies. Evidence suggests that maternal cadmium exposure, facilitated through methods such as intraperitoneal injection in rodent models, results in negative consequences for offspring, including modifications in gene expression and compromised lung structure and functionality. Cadmium is primarily absorbed via the respiratory system, with inhalation associated with a range of respiratory ailments, including chronic lung diseases and lung cancer. Additionally, cadmium exposure has been linked to complications during pregnancy, such as miscarriage and low birth weight, likely due to mechanisms involving endocrine disruption and oxidative stress. This study underscores the necessity of comprehending cadmium's impact on fetal development and the potential protective effects of nutrients like vitamin D and magnesium during gestation. Given the strong association between cadmium exposure and adverse health effects, further investigation is warranted to clarify these impacts' underlying mechanisms and identify preventive measures. This paper offers a thorough overview of cadmium influence on the development of the fetal respiratory system and proposes future research directions in this vital area of public health.

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