Review

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The impact of heavy metals exposure on male fertility: a scoping review of human studies

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Abstract

Introduction: Male infertility is a critical global health issue, with environmental and occupational exposure to heavy metals, such as lead (Pb), cadmium (Cd), mercury (Hg), and arsenic (As), impacting male reproductive health. This scoping review aims to evaluate the effects of heavy metal exposure on semen parameters.

Content: This study adhered to the 2020 PRISMA framework. A broad literature search was performed on January 2025, using Embase, PUBMED, and Scopus. A comprehensive literature search was performed using PubMed, Embase, and Scopus on January 12, 2025, using a combination of Medical Subject terms and keywords.

Summary: Of the 1,709 identified studies, 21 met the inclusion criteria and were analyzed. Findings indicate that lead exposure negatively impacts sperm concentration, motility, and morphology, primarily through oxidative stress and enzymatic inhibition. Cadmium disrupts the blood-testis barrier and acrosomal function, leading to sperm abnormalities. Arsenic exposure is linked to oxidative stress, apoptosis, and impaired sperm motility.

Outlook: The cumulative evidence supports a strong association between heavy metal exposure and male infertility. This review underscores the need for stricter occupational safety regulations and environmental policies to mitigate heavy metal exposure.

Keywords: heavy metals; male infertility; semen parameters; lead; cadmium

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Introduction

Male infertility is a significant global health concern, affecting approximately 7 % of the male population and contributing to nearly half of all cases of couple infertility [1]. Estimates suggest that 50–80 million people worldwide experience infertility, with male factors accounting for 20–30 % of cases [2]. In most instances, semen impairment is classified as non-obstructive, resulting from impaired testicular sperm production, which necessitates distinct diagnostic and therapeutic approaches [3, 4].

This clinical condition is multifactorial, arising from genetic abnormalities, hormonal disruptions, and lifestyle factors. Increasing evidence suggests that environmental exposure plays a key role in its prevalence [5–7]. In particular, exposure to environmental pollutants, such as pesticides, endocrine-disrupting chemicals, and heavy metals, is associated with adverse effects on male reproductive health. These toxic substances can impair spermatogenesis, reduce sperm quality, and increase sperm DNA fragmentation, ultimately contributing to infertility [8, 9]. Heavy metals, in particular, represent a significant threat to male reproductive health due to their persistent accumulation in the environment from industrial and agricultural activities. Unlike degradable pollutants, heavy metals accumulate over time, posing long-term ecological and human health risks [10]. While some heavy metal ions serve as essential trace elements at low concentrations, they become toxic at higher levels, inducing oxidative stress, impairing testicular function, and causing irreversible reproductive damage. Studies indicate that heavy metal exposure negatively affects male

fertility by reducing sperm count, altering sperm morphology, and decreasing fertilization potential [11]. Furthermore, reproductive toxicology research suggests that these environmental factors extend beyond individual health, impacting population health and demographic stability [12].

This review aims to synthesize current knowledge on the impact of environmental and occupational exposure on male infertility, highlighting the mechanisms through which pollutants disrupt reproductive health and discussing potential strategies for mitigating these adverse effects.

Materials and methods

Evidence acquisition

Literature search

In this study, we performed a scoping review evaluating the influence of various metals (including Lead [Pb], Cadmium [Cd], Arsenic [As], and Mercury [Hg]) on semen parameters.

A comprehensive literature search was performed on 12th January 2025, using PubMed, Embase and Scopus. Medical Subject Heading (MeSH) terms and keywords were used as follows: ("male fertility" OR "sperm quality" OR "semen parameters" OR "male reproductive health" OR "male infertility") AND ("environmental exposure" OR "occupational exposure" OR "pollution" OR "toxins" OR "endocrine disruptors" OR "heavy metals" OR "air pollution" OR "chemical exposure" OR "industrial chemicals") AND ("impact" OR "effects" OR "association" OR "risk factors"). There was no date restriction.

Selection criteria

The PECOS (Patient Exposure Comparison Outcome Study type) model was used to frame and answer the clinical question. *Population*: adult men with no diagnosis of infertility; *Exposure*: environmental or occupational exposure to Pb, Cd, As or Hg*; Comparison*: non-exposed males; *Outcomes*: Semen parameters (semen volume; sperm total count, sperm concentration, sperm vitality, sperm total, and progressive motility; sperm normal morphology; seminal viscosity); *Study type*: Observational studies.

Study screening and selection

Two distinct authors screened all gathered records through Covidence Systematic Review Management®. A third author solved discrepancies. Studies were accepted and included based on PECOS eligibility criteria. Reviews, meeting abstracts, letters to the editor, case reports, non-English articles and editorials were also excluded. The full text of the screened papers was selected if deemed relevant to the aim of this study. Articles solely focused on epidemiological investigations or systems unrelated to fertility were excluded. Studies focusing on sex chromosome ratio in spermatozoa as the only outcome of interest were also not accepted.

Results

Literature screening

The initial literature search yielded a total of 1,709 articles. Following the removal of 498 duplicate records, 1,211 unique studies remained for screening. Of these, 1,074 articles were excluded after title and abstract screening due to irrelevance to the study's objectives. The full texts of the remaining 137 manuscripts were subsequently assessed, resulting in the exclusion of an additional 116 studies. Ultimately, 21 studies met the inclusion criteria and were incorporated into the review. Figure 1 shows the 2009 PRISMA flow diagram. Ten studies evaluated semen parameters following lead exposure [13–21], four assessed the effects of cadmium exposure [22–25], five examined mercury exposure [26–30], and another four investigated arsenic exposure [24, 26, 30, 31]. Table 1 summarizes the studies characteristics.

Lead

Lead has been extensively studied as a toxic chemical agent, particularly in occupational settings. The permissible exposure limit (PEL) for lead is set at an average of 50 µg/dL over an 8 h period [32]. The toxicity of lead is multifaceted due to its wide-ranging interactions within the body. One of its key effects is the disruption of ion channels, particularly certain isoforms of the K^+ channel, which are crucial in the early stages of the acrosomal reaction [33]. Additionally, lead inhibits enzymatic activity, as evidenced by a 68 % reduction in creatine kinase levels [34]. It also induces oxidative stress, leading to decreased antioxidant enzyme activity and damage to nucleic acids and polyunsaturated fatty acids (PUFAs) in cell membranes [35].

Elevated lead concentrations in the seminal plasma of infertile men have been positively correlated with fructose levels and negatively associated with acid phosphatase and γ-glutamyl transferase (γ-GT) activity [36]. In infertile smokers, lead exposure has been linked to reduced glutathione (GSH) levels, decreased glutathione S-transferase

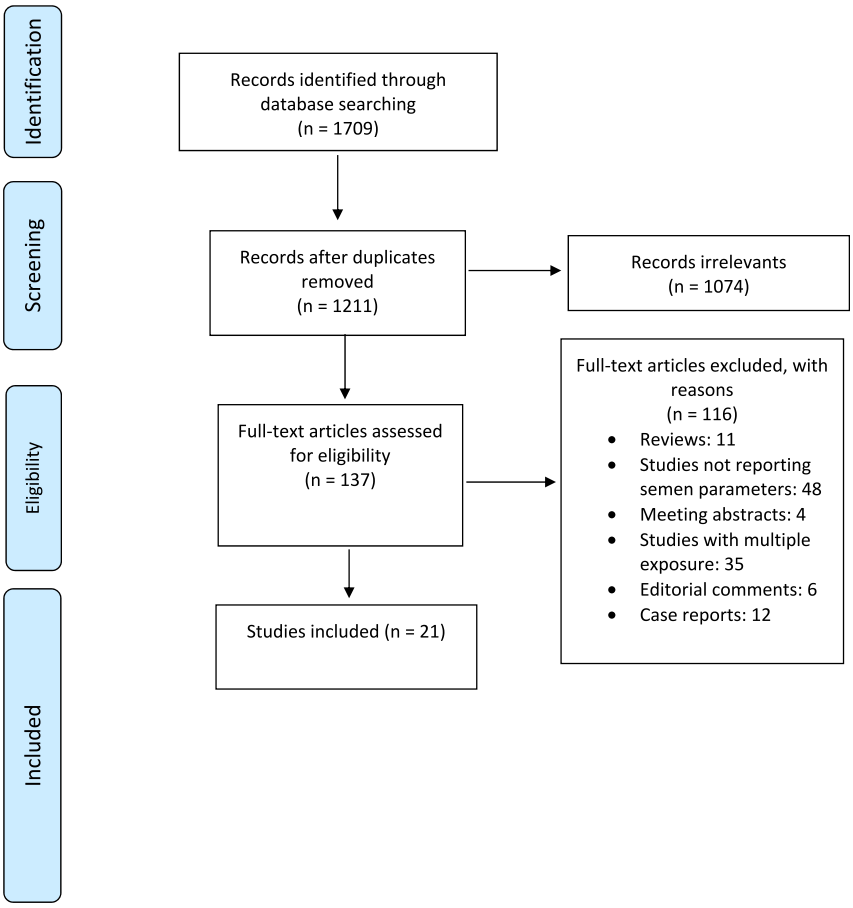

Figure 1: PRISMA 2009 flow diagram.

(GST) activity, increased reactive oxygen species (ROS), and elevated lipid peroxidation [37].

The timeline of lead-induced pathogenesis remains uncertain. Indirect effects, resulting from increased lead concentration in seminal vesicles, may appear within days, whereas direct effects – such as disruption of spermatogenesis – could take several weeks (up to 12) to manifest [38]. However, the latter is considered less likely due to the protective role of the blood-testis barrier, which limits lead penetration [39].

Observational studies suggest that the clinical manifestations of lead toxicity are dose-dependent. Chronic exposure, even at low doses, negatively impacts sperm concentration ($p<0.01$), motility ($p=0.029$), morphology ($p<0.01$), and viability ($p<0.01$) [13]. However, Xu et al. reported no significant correlations at a blood lead concentration (BPb) of 0.78 µg/dL [14]. When its levels exceed 1 µg/dL, all semen quality parameters decline, particularly progressive sperm motility ($\beta=-2.12$, $p<0.05$) and morphology ($\beta=-1.42$, $p<0.05$), and Pb in seminal fluid is also associated with increased nuclear chromatin condensation (NCD) ($\beta=0.264$, $p<0.05$) [15]. Telisman et al. found that at BPb levels of 4.9 µg/dL, there is an increase in morphologically abnormal sperm ($\beta=12.638$, $p<0.001$) with higher lead exposure [16].

Despite the removal of lead from consumer products such as gasoline and paint, it remains widely used in industrial processes, including battery manufacturing, soldering, metal alloy production, and plastics processing [40]. Consequently, occupational BPb levels are generally higher than those in the general population, with workers displaying significantly elevated blood lead concentrations relative to seminal plasma levels. Even at exposure levels below 50 µg/dL, semen quality remains compromised, with significant reductions in sperm concentration ($p<0.02$), motile sperm count ($p<0.05$), and viability ($p<0.05$) [17]. Mahmoud et al. reported a decrease in sperm concentration among 68 workers from a lead smelter ($p=0.028$) [18]. A dose-dependent negative correlation has been observed between lead exposure and these parameters in a multicentric analysis, with a 49 % reduction in median sperm concentration among men with blood lead concentrations exceeding 50 µg/dL compared to those in the baseline group with levels below 10 µg/dL ($p<0.05$) [19]. A cross-sectional study conducted in Poland observed a decrease in total sperm motility and an increase in lipid peroxidation in seminal plasma, as

Table 1: Studies concerning the effects of lead on male fertility.

Reference	Study type	Metal	Population, n	Seminal metal concentration	Reproductive effects
Morán-Martínez et al. [13]	Cross-sectional	Lead	20 residents near a metallurgical zone, 27 controls	10 nmol/L	Reduced sperm concentration, motility, normal morphology, and viability
Xu et al. [14]	Cross-sectional	Lead	56 non-smoking subjects	0.78 µg/dL	No association with semen quality
Hernandez-Ochoa et al. [15]	Cross-sectional	Lead	68 residents of region Lagunera, Mexico	9.3 µg/dL	Reduced progressive sperm motility, concentration, morphology, and viability
Telisman et al. [16]	Cross-sectional	Lead	240 Croatian males	4.9 µg/dL	Increased immature sperm concentration and proportion of pathological sperm
Telisman et al. [17]	Cross-sectional	Lead	98 industrial workers, 51 reference subjects	37 µg/dL	Decreased sperm concentration, total sperm count, progressive motility, viability, and normal morphology
Mahmoud et al. [18]	Cross-sectional	Lead	68 healthy Belgian workers, 91 controls	31 µg/dL	Reduced sperm concentration
Bonde et al. [19]	Cross-sectional	Lead	503 lead industry workers	19 workers: 0–10 µg/dL, 52: 11–25 µg/dL, 73: 26–40 µg/dL, 49: >40 µg/dL	Progressive decline in sperm concentration with increasing blood lead levels
Kasperczyk et al. [20]	Cross-sectional	Lead	49 employees of zinc and lead metal works, 14 controls	29 workers: BPb=40–81 µg/dL, 20 workers: BPb=25–40 µg/dL	Reduced percentage of motile spermatozoa in highly exposed individuals
Eibensteiner et al. [21]	Cross-sectional	Lead	18 traffic police officers	Mean: 48.5 µg/dL; 8 officers: <40 µg/dL, 10 officers: >40 µg/dL	Reduced sperm viability and motility
Jurasovic et al. [22]	Cross-sectional	Cadmium	123 Croatian men with no occupational metal exposure	B 0.85 µg/L	No correlation between blood cadmium (BCd) levels and semen parameters
Wang et al. [23]	Cross-sectional	Cadmium	1,247 men	–	Inverse correlation between cadmium levels and total sperm motility
Pant et al. [24]	Cross-sectional	Cadmium, arsenic	60 men	49 µg/L	Reduced sperm motility and concentration
Jeng et al. [25]	Cross-sectional	Cadmium, arsenic	213 healthy men	Cd: 0.5 µg/g Cr, As: 91.1 µg/g Cr	Cd: reduced sperm viability; As: reduced sperm concentration
Choy et al. [26]	Case-control	Mercury	111 men in an IVF unit	41.4 nmol/L	Higher semen mercury levels associated with abnormalities in sperm morphology and motility
Leung et al. [27]	Case-control	Mercury	59 men in an IVF unit	High exposure group: 68.9 nmol/L, low exposure group: 31.2 nmol/L	No significant difference in semen parameters between exposure groups
Rignell-Hydbom et al. [28]	Cross-sectional	Mercury	189 fishermen	2.25 µg/L	No alterations in semen parameters
Mocevic et al. [29]	Cross-sectional	Mercury	529 healthy men	7.3 µg/L	No alterations in semen parameters
Zeng et al. [30]	Cross-sectional	Mercury	394 men	U 1.21 µg/g Cr	No alterations in semen parameters
Zeng et al. [31]	Cross-sectional	Arsenic	394 healthy men	U 25.09 µg/g Cr	No alterations in semen parameters
Shen et al. [30]	Cross-sectional	Arsenic	140 exposed men, 151 unexposed controls	U 95.6 µg/g Cr	Reduced sperm volume, concentration, and motility

U, urine level; B, blood level.

indicated by a 56 % higher malondialdehyde (MDA) concentration in the healthy group (p=0.010) [20]. Furthermore, sperm cell motility after 1 h demonstrated an inverse correlation with blood lead levels (PbB) (R=−0.32, p=0.011). A noteworthy study by Eibensteiner et al. examined traffic police officers in Arequipa, Peru, who were exposed to high

levels of lead from gasoline fumes [21]. They reported a mean BPb level of 48.5 µg/dL, which was associated with reductions in sperm viability (p<0.01) and motility (p=0.03). However, Wijesekara et al. found no significant decrease in sperm concentration, motility, vitality, and morphology at seminal lead levels of 41.1 µg/dL [22].

Cadmium

Cadmium is a heavy metal and a significant environmental toxicant with carcinogenic properties, ranking seventh on the CERCLA Priority List of Hazardous Substances [41]. Although its precise etiopathogenesis remains unclear, cadmium disrupts male reproductive health through multiple pathways.

One of its primary effects is the disruption of the blood-testis barrier. Cadmium inhibits the assembly of Sertoli cells via tight junctions in a dose-dependent manner [42], not through direct cytotoxicity but by altering the synthesis and expression of key proteins. For instance, cadmium reduces occludin [43] and focal adhesion kinase [44] levels, leading to their redistribution and impairing the Sertoli cell–spermatid interface. This disruption negatively impacts spermatogenesis [45]. Additional mechanisms include cadmium-induced oxidative stress, which contributes to abnormal sperm morphology [46], and cadmium binding to specific isoforms of L-type calcium channels, impairing the acrosomal reaction [33]. Furthermore, cadmium exposure promotes mitochondrial fission, further compromising sperm function [47].

Occupational exposure to cadmium is particularly common in industries producing batteries, pigments, ceramics, plastic stabilizers, and fertilizers. Until 2008, the Agency for Toxic Substances and Disease Registry (ATSDR) considered the evidence linking cadmium exposure to male infertility insufficient [48]. However, more recent studies – especially those involving non-occupationally exposed men – suggest a dose-dependent relationship between cadmium levels and reproductive impairment.

Research findings on blood cadmium levels below 1 µg/L remain inconclusive. While some studies indicate that cadmium exposure affects the hypothalamic-pituitary-gonadal (HPG) axis, no significant changes in semen parameters have been observed at these lower concentrations [23].

Further evidence is provided by a study conducted by Wang et al., which examined 1,247 men with unexplained infertility and identified an inverse correlation between cadmium levels and both total sperm motility (p trend=0.02) and sperm concentration (p trend=0.001) [24]. Similarly, a case-control study by Pant et al. reported a negative correlation between cadmium levels and sperm motility (β=−3.38, p<0.01) as well as sperm concentration (β=−2.80, p<0.003) [25].

Additionally, at urinary cadmium concentrations of 0.5 µg/g creatinine, reduced sperm viability was observed (Pearson coefficient =−0.216, p=0.006) [26].

Mercury

Mercury is a widely distributed heavy metal distinguished by its unique property of being liquid at standard temperature and pressure. It naturally occurs in three forms: elemental, inorganic, and organic [49]. The routes of non-occupational exposure vary depending on its form. Elemental mercury exposure primarily arises from dental amalgams, pharmaceutical applications, and cosmetic products, whereas organic mercury exposure is largely associated with the consumption of fish, shellfish, and marine mammals from specific geographical regions [50].

While the toxic effects of mercury on the nervous, muscular, and integumentary systems are well established, its impact on male fertility remains a subject of debate. Mercury primarily induces oxidative stress, as evidenced by reduced levels of superoxide dismutase (SOD) and glutathione (GSH), along with increased lipid peroxidation. These biochemical changes contribute to DNA fragmentation, impaired acrosomal reactions, reduced sperm viability, and increased apoptosis in testicular tissue [51, 52]. Furthermore, Ghaffari et al. demonstrated that mercury inhibits creatine kinase activity, leading to decreased energy production in sperm tails and, consequently, reduced sperm motility [53].

Occupational exposure to metallic mercury is most commonly linked to industrial activities, while inorganic mercury exposure is predominantly associated with battery and pigment production.

Despite strong laboratory evidence demonstrating mercury's biological effects, its clinical impact on male fertility remains inconclusive. Choy et al. reported a negative correlation between seminal mercury concentrations and both normal sperm morphology (r=0.26, p=0.02) and sperm motility (r=−0.21, p=0.03) [27]. However, no association was found between mercury levels and either the percentage of motile sperm or overall sperm concentration. Conversely, a retrospective study by Leung et al. found no significant differences in semen quality parameters – including sperm concentration, motility, and morphology – between individuals with high and normal mercury levels [28].

Similarly, studies on fishermen, a population with higher mercury exposure due to dietary intake, reported no significant abnormalities in semen parameters at a median

mercury concentration of 2.25 µg/L [29]. Even at elevated blood and urinary mercury levels, no significant changes in sperm quality were observed [30, 31].

Arsenic

Arsenic, a metalloid widely distributed in the Earth's crust, is present in significant quantities in the groundwater of many countries [54]. In its inorganic form, particularly in its trivalent state, arsenic exhibits high toxicity [55]. Exposure to arsenic induces oxidative stress, as evidenced by increased ROS production and lipid peroxidation, along with a reduction in non-protein sulfhydryl (NPSH) groups and SOD activity [56]. These biochemical alterations contribute to sperm immotility following GSH depletion [57], G2/M phase cell cycle arrest, and increased p53 phosphorylation, ultimately leading to apoptosis [58]. Notably, an association between environmental arsenic exposure and polymorphisms in GSTs was noted among different ethnic groups, highlighting potential genetic susceptibility [59].

Arsenic also exerts direct toxic effects on Sertoli cells, impairing male reproductive function through multiple mechanisms. It reduces the expression of key genes involved in cell adhesion, such as *CLDN11* and *OCLN* [60], inhibits androgen receptor recruitment to its target gene enhancer [61], and increases the activity of caspases −3, −8, and −9. This caspase activation, in conjunction with ROS generation, promotes apoptotic cell death [58].

Occupational exposure to arsenic is most common in industries related to mineral extraction and processing, such as metal mining, smelting, fossil fuel combustion, and the production of wood preservatives. In these settings, workers are primarily exposed through the inhalation of arsenic-containing air and dust [31]. Notably, men with unexplained infertility have been found to exhibit higher levels of arsenic metabolites and an increased primary arsenic methylation index, suggesting a potential biomarker for arsenic-related reproductive toxicity [62].

Despite significant advancements in understanding arsenic's mechanisms of toxicity, human observational studies remain limited. Similar to other heavy metals, arsenic's effects on semen parameters are concentration dependent. While no clinical correlation was observed at a urinary arsenic concentration of 25 µg/g creatinine [30], Jeng et al. reported a higher prevalence of sperm concentrations (Pearson correlation coefficient =−0.163, p=0.036) at this level [26]. At 95.6 µg/g creatinine, Shen et al. documented reductions in semen volume, sperm concentration, and motility, as well as a significant correlation between inorganic arsenate exposure and infertility risk, with the odds ratio increasing from 4.9 in the lowest quartile of exposure to 13.6 in the highest quartile [63]. Additionally, arsenic exposure has been linked to impaired progressive (p=0.001) and total (p=0.002) sperm motility [24].

Discussion

This review reinforces the growing body of evidence linking environmental and occupational exposure to heavy metals with adverse effects on male fertility. Consistent with previous research, the findings demonstrate that these toxicants negatively impact key semen parameters, including sperm concentration, motility, morphology, and DNA integrity.

Lead exposure, in particular, is strongly associated with oxidative stress, enzymatic inhibition, and sperm dysfunction, supporting prior studies that have documented a dose-dependent decline in semen quality even at relatively low exposure levels. This underscores concerns regarding occupational hazards and the continued use of lead in industrial processes. Similarly, cadmium disrupts the blood-testis barrier, oxidative homeostasis, and acrosomal function, further reinforcing its toxicological impact on male reproductive health.

The effects of mercury on male fertility remain inconclusive. While laboratory studies provide substantial evidence of its detrimental effects on sperm function, human studies yield inconsistent findings, highlighting the need for well-controlled investigations to clarify its reproductive risks. Meanwhile, arsenic exposure is clearly associated with sperm damage and apoptosis, supporting epidemiological data linking arsenic-contaminated groundwater to reduced male fertility.

Overall, this review underscores heavy metal exposure as a significant reproductive health risk, emphasizing the urgent need for stricter occupational safety regulations, enhanced environmental monitoring, and further research to establish exposure thresholds that minimize fertility impairment.

Several limitations should be considered when interpreting these findings. A primary limitation is the reliance on cross-sectional studies, which restricts the ability to assess long-term trends in heavy metal exposure and its reproductive consequences, thereby limiting causal inferences. Additionally, while toxicity mechanisms such as oxidative stress and DNA fragmentation are well-supported by *in vitro* and animal studies, the absence of human clinical trials and randomized controlled studies precludes definitive conclusions regarding the impact of heavy metals on male infertility. Another limitation of this review is its exclusive focus on semen parameters, without considering

DNA fragmentation or reproductive outcomes. This narrow scope may hinder a comprehensive assessment of male fertility, as DNA integrity is a crucial factor in evaluating the full effects of environmental exposures on reproductive health [1, 64, 65]. Moreover, existing literature presents conflicting evidence regarding the extent to which metal exposure compromises the ability to achieve pregnancy, further complicating the interpretation of findings [66, 67]. Finally, many studies included in this review fail to adequately control for confounding factors such as lifestyle habits and overlapping environmental exposures, making it challenging to isolate the specific effects of lead, cadmium, mercury, and arsenic on male fertility [68–70].

Conclusions

This review highlights the significant impact of environmental and occupational exposure to heavy metals on male reproductive health, demonstrating that these toxicants adversely affect key semen parameters – including sperm concentration, motility, morphology, and viability – ultimately contributing to male infertility. While exposure to lead and cadmium shows a clear and consistent association with deteriorating sperm quality, the reproductive toxicity of mercury remains inconclusive, warranting further investigation. Likewise, arsenic exposure has been linked to sperm dysfunction and apoptosis; however, additional longitudinal studies are needed to establish definitive exposure thresholds and elucidate the underlying mechanisms.

The growing body of evidence on the reproductive hazards of heavy metal exposure underscores the urgent need for public health interventions. Strengthening occupational safety regulations, enhancing environmental monitoring, and implementing policies to minimize human exposure to these toxicants are critical to mitigating their effects on male fertility. Addressing existing knowledge gaps will support the development of targeted preventive and therapeutic strategies to protect reproductive health in exposed populations.

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