

## REPRODUCTIVE TOXICITY OF METALS IN MEN

Alica PIZENT, Blanka TARIBA, and Tanja ŽIVKOVIĆ

*Institute for Medical Research and Occupational Health, Zagreb, Croatia*

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A combination of genetic, environmental and lifestyle factors contributes to adverse effects on the reproductive health in men. Metals are pervasive in food, water, air, tobacco smoke, and alcoholic beverages. Experimental studies suggest that many metals have adverse effects on the male reproductive function. However, information about reproductive effects of human exposure to metals is scarce and/or inconsistent. This review summarises the information from epidemiological studies of the effects of metal exposure on reproductive function in men. Factors capable of affecting these relationships were identified and discussed. A particular attention is given to the studies considering influence of concomitant exposure to various metals.

These studies have generally confirmed that even moderate- to low-level exposure to lead affects certain reproductive parameters, and that exposure to cadmium affects the prostate function and serum testosterone levels. Adverse effects of mercury, manganese, chromium and arsenic on semen quality and altered serum hormone are less well documented. There is no clear evidence that boron exposure may impair reproductive health in men. Only a few studies have investigated reproductive effects of concomitant exposure to several metals and controlled for potential confounders. Future studies should consider the contribution of combined exposure to various metals and/or other factors that may influence individual susceptibility to reproductive health impairment in men.

**KEY WORDS:** *human semen quality, metals, metalloids, metal interactions, sex hormones*

In 1992, a meta-analysis of data from international literature by Carlsen et al. (1) indicated a significant deterioration in the reproductive health of otherwise normal men in many countries over the period 1938 to 1990. It prompted other researchers to evaluate their own data. Several studies established an increasing incidence of various abnormalities of the human reproductive system, including a decreased sperm count and an increased incidence of testicular and prostate cancer (2-7), but also great differences among countries and different locations within a country. This has triggered an increasing interest in the possible causes of these abnormalities and factors that contribute to this deterioration and the geographical differences, including environmental and lifestyle factors (8-13).

Metals are everywhere, in food, dietary supplements, water, air, alcoholic drinks, and tobacco. Cigarette smoke contains about 30 metals, of which cadmium, arsenic, and lead are in the highest concentrations, and cadmium body burden in smokers is about double that of non-smokers (14). Alcoholic beverages including wine can be contaminated with metals in concentrations exceeding the allowable limits and causing toxic effects, particularly in heavy drinkers (15-17).

Most reports on the reproductive toxicity of metals are from experimental animal studies, which usually involve high-dose and/or short-term exposure not applicable to common human exposure situations. The human male has a relatively low fertility potential compared with other mammals and is much more

susceptible to metal toxicity. Therefore, epidemiological studies are needed to validate the effects identified in experimental models. Data on reproductive toxicity in men are scanty for most metals (18-22), and usually limited by inadequate controls and adjustments for the influence of potentially confounding variables.

The aim of this review is to provide a summary of epidemiological research of the effects of metal exposure on reproductive health in men, and particular attention is given to the studies considering the combined influence of several metals and lifestyle factors (e.g., smoking habits and alcohol consumption). We will also discuss other factors that can modify metal status and its effects on the reproductive function in men.

## SOURCES OF METAL EXPOSURE

Men are inevitably exposed to metals due to their ubiquity in nature, wide use in industry and long-term persistence in the environment. The information on the most important occupational and environmental sources of metal exposure has mainly been collected from the toxicological profiles issued by the Agency for Toxic Substances and Disease Registry (ATSDR) (23-29), unless stated otherwise.

Lead is used for ammunition, batteries, solder, and X-ray shields. Sources of occupational exposure include lead mining, refining, smelting, construction work, paint removal, demolition, maintenance of bridges and water towers, car repair, and recycling. Environmental lead exposure has dropped in recent decades thanks to the dominant use of unleaded petrol and the ban of lead-based paint and lead solder in food cans. The general population can be exposed to lead in food and drinks, including lead-contaminated folk remedies (30-32), drinking water (33), and wine (15-16). Strongly acidic beverages (such as wine, fruit juices, and soft drinks) and food can be contaminated with lead if stored or served in leaded crystal glassware or lead-glazed ceramics.

Cadmium is used in the production of nickel-cadmium batteries, pigments (bright yellow, orange, red, and maroon dyes), ceramics, plastic stabilisers, and fertilisers. Increased production of CdSe/CdTe-based photovoltaic solar cells for alternative energy production and the use of CdSe/CdTe in nanomaterials for biological applications in the past decades may have contributed to increased human exposure to cadmium (34). Cigarette smoke is one of the most

important sources of cadmium exposure in the general non-occupationally exposed population. In non-smokers, the main source of cadmium is food, particularly cereals such as rice and wheat, green leafy vegetables, potato, and offal products such as liver and kidney.

Mercury exists in several forms. Metallic mercury is used for the extraction of gold and silver from ores, in the production of chlorine gas and caustic soda, in thermometers, barometers, fluorescent light bulbs, and some electrical and electronic switches, as a component in dental amalgam fillings, and in some herbal or religious remedies. Organic and inorganic compounds of mercury are used as catalysts for polyurethane and other polymer production, in the production of fungicides, pigments, cosmetics (e.g. skin whitening cream and mascara), and pharmaceuticals (e.g. vaccine preservatives such as thiomersal and eye drops). The most common organic compound of mercury is methylmercury (MeHg). The general population is exposed to MeHg mainly through diet, especially through freshwater (e.g. pike and bass) and marine (e.g. shark, swordfish, barracuda, large tuna) fish.

Organic manganese compounds are used in the production of pesticides, whereas methylcyclopentadienyl manganese tricarbonyl (MMT) is used as a petrol additive. Manganese can also be found in grains and cereals, and in high amounts in tea.

Arsenic is a metalloid. Inorganic arsenic compounds are highly toxic, whereas organic compounds are harmless. Elemental arsenic is used as an alloying element in ammunition and solders. Inorganic arsenic is used to preserve wood. The use of inorganic arsenic for pesticides is no longer permitted. Organic compounds of arsenic are used as herbicides and as antimicrobial additives for animal and poultry feed. Fish and seafood may contain high levels of harmless organic forms of arsenic. Diet is generally the main source of arsenic. The general population may be exposed to high levels of inorganic arsenic in drinking water from the areas that contain high natural levels of arsenic in rock, e.g. several localities in East Croatia (35).

Chromium is present in several forms. Metal chromium (0) is used in steel production, whereas chromium (VI) and chromium (III) are used for chrome plating, dyes and pigments, leather tanning, and wood preserving. Chromium (VI) compounds are more toxic than chromium (III) compounds. Chromium (III) occurs naturally in the environment and is an essential nutrient, present in food.

Boron in the form of borates or boric acid is widely used in the production of sodium perborate bleaches, soaps and detergents, insulation materials, fiberglass, borosilicate glass, fire retardants, wood preservatives, adhesives, pesticides, soldering and welding fluxes, and cosmetics. As an antiseptic and antibacterial compound, boric acid can be used to wash the eyes and treat yeast and fungal infections. Boron can mainly be found in nuts, fruits, and vegetables.

## FACTORS INFLUENCING HEALTH OUTCOMES OF HUMAN EXPOSURE TO METALS

Men are usually exposed to many metals and other agents that act together resulting in adverse health effects or increased sensitivity to these effects. It is often difficult to correlate specific metal exposure to specific effect because of the complexity of these relationships. Many factors can influence health outcomes of human exposure to metals.

Some of them are metal speciation (chemical form), dose, timing, routes and duration of exposure, dose-response relationship, bioavailability, and distribution and accumulation of metals in various organs. Response to metal exposure also depends on the age, sex, health status, dietary habits, use of medications and/or supplements, physical activity, and concomitant exposure to other metals and/or chemicals (36-37).

Metals can interact additively, synergistically, or antagonistically and affect each other's absorption, distribution, and excretion. Toxic metals can interfere with the metabolism of essential metals and reduce their concentration in the organism or decrease their bioavailability (36, 38-40). For example, competition between lead and/or cadmium and zinc for the same binding sites in enzymes, proteins, and transporters, can change enzyme activity, affect the structure and/or function of cell membranes, induce oxidative stress and apoptosis, and inhibit DNA and RNA synthesis and repair. This may have serious consequences on cell growth, development, and differentiation. On the other hand, essential metals (e.g., zinc and selenium) may decrease the absorption and retention of toxic metals and prevent their toxic effects. Moreover, metals have a significant role in the antioxidant system, adaptive response, and genetic repair system. Therefore, the interaction between various toxic and/or essential metals

could be particularly important for the final health outcomes of metal exposure. These interactions contribute to interindividual differences in susceptibility to adverse effects of metals in men (36).

One of the factors responsible for these differences in susceptibility to metal exposure between individuals living in the same or similar environments is genetic polymorphism. Several recent attempts to investigate the influence of genetic polymorphisms on metal metabolism have identified varieties in genetic coding for proteins involved in metal absorption, retention, biotransformation, transport, and storage, for proteins comprising plasma membrane ion channels, and for enzymes protecting against oxidative stress. However, only a few studies have assessed the potential effects of these polymorphisms on the relationship between metal exposure and health outcomes in men (reviewed in 18 and 20).

## TARGETS AND MECHANISMS OF METAL ACTION

Metals may affect the male reproductive system directly, when they target specific reproductive organs, or indirectly, when they act on the neuroendocrine system.

These effects can be long lasting and irreversible if Sertoli cells are disrupted during foetal development. The number of Sertoli cells determines the number of sperm produced in adulthood, because each Sertoli cell can support only a finite number of germ cells that develop into sperm. According to Sharpe et al. (41), Sertoli cells proliferate during the foetal, neonatal and pre-pubertal period, and each of these periods is particularly sensitive to the adverse effects of metals.

The disruption of spermatogenesis in men (Table 1) at any stage of cell differentiation can decrease the total sperm count, increase the abnormal sperm count, impair the stability of sperm chromatin or damage sperm DNA (43). Accumulating in the epididymis, prostate, vesicular seminalis or seminal fluid, metals may impair progressive sperm motility (44). In addition, metals can cause hormonal imbalance by affecting the neuroendocrine system, disrupting the secretion of androgens from Leydig cells or Inhibin B from Sertoli cells (45).

There is growing evidence that oxidative stress is implicated in the pathogenesis of male infertility (19,

46-50). It is known that human spermatozoa are particularly vulnerable to oxidative stress. An excessive generation of reactive oxygen species (ROS) in the spermatozoa results in the peroxidation of polyunsaturated fatty acids within their plasma membrane (51). Several metals, including iron, copper, nickel, lead, and cadmium, may increase ROS production, decrease glutathione and other antioxidant levels, enhance the lipid peroxidation of the cell membrane, cause apoptosis, and contribute to the oxidative damage of DNA (52-55). Damage to the sperm membrane reduces sperm's motility and ability to fuse with the oocyte, whereas damage to sperm DNA compromises paternal genomic contribution to the embryo (49) and increases the risk of infertility, miscarriage, or serious disease in the offspring (56).

Some malformations of the male reproductive system, such as cryptorchidism, hypospadias, and prostate and testicular cancers may originate from exposure to endocrine disruptors (Table 1). Cadmium, mercury, lead, and arsenic are suspected to affect the endocrine system (58-59). Evidence is usually limited to animal data or to *in vitro* studies (59-61). The clinical and epidemiological findings are scarce and controversial, and often difficult to interpret because of multiple exposures to different agents and latency of effects.

## REPRODUCTIVE EFFECTS OF METAL EXPOSURE

The assessment of male reproductive capacity usually includes the following reproductive parameters:

- parameters of semen quality (e.g. semen volume, sperm concentration and count, motility, viability, and morphology of sperm),
- parameters of the secretory function of the prostate and seminal vesicles in seminal plasma (e.g. zinc, fructose), and
- parameters of reproductive endocrine function in serum (i.e. sex hormones; e.g. follicle-stimulating hormone, luteinizing hormone, testosterone, and oestradiol).

Metals can affect the testis size, semen quality, the secretory function of the prostate and seminal vesicles, the reproductive endocrine function and can lead to the loss of fertility and libido or to impotence (18-22). Moreover, exposure to cadmium, lead, and inorganic

arsenic may contribute to prostate cancer development (62-66). Environmental exposure to cadmium and/or lead is associated with increased serum prostate specific antigen (PSA, Table 1) (67-68). Most reports on detrimental influence of metals on reproductive health in men are from occupational studies with high-levels exposure (18-20).

### *Effects of occupational exposure to metals on reproductive parameters*

In men occupationally exposed to lead, blood lead levels equal to or higher than  $400 \mu\text{g L}^{-1}$  have been associated with reduced sperm count, poor semen motility, and abnormal sperm morphology, particularly of the sperm head (69-78). Effects on the reproductive endocrine function have been less consistent (71, 74, 79-83). Reduced sperm count and concentration, and lower motility were found in lead workers with blood lead levels lower than  $400 \mu\text{g L}^{-1}$  (78, 84-85). These adverse effects of lead exposure were confirmed in regression models adjusted for the influence of age, smoking, alcohol, blood cadmium, and serum copper and zinc (78). In addition, a better correlation of reproductive parameters with the activity of delta-aminolevulinic acid dehydratase (ALAD) in blood, which better reflects long-term cumulative lead exposure than blood lead level, indicated that the reproductive effects were at least partly mediated through lead interference with zinc metabolism (78).

Information regarding reproductive effects in male workers occupationally exposed to cadmium is limited and insufficient to estimate a quantitative dose-response relationship or no-adverse-effect exposure thresholds. For example, in smelter workers exposed to cadmium and control subjects, significantly higher serum testosterone was found in men with urinary cadmium levels of (10 to 20)  $\mu\text{g g}^{-1}$  creatinine than in men with (0 to 2)  $\mu\text{g g}^{-1}$  or (2 to 5)  $\mu\text{g g}^{-1}$  creatinine (85). In men with urinary cadmium levels  $>20 \mu\text{g g}^{-1}$  creatinine, serum levels of the luteinising hormone were significantly higher, but testosterone levels did not differ significantly. Other studies showed no significant reproductive effect of occupational exposure to cadmium (86-87).

A few studies reported the effects of occupational exposure to mercury, manganese, chromium and boron on reproductive health in men and the available data are inconsistent.

In chloralkali workers with mean urinary mercury of  $27 \mu\text{g g}^{-1}$  creatinine and mean blood mercury of  $9.5$

$\mu\text{g L}^{-1}$ , exposed for an average of 10 years to mercury vapour, cumulative mercury exposure positively correlated with serum total testosterone, but not with free testosterone (88). In another group of workers with urinary mercury of  $71.2 \mu\text{g g}^{-1}$  creatinine, no significant association was found between urinary mercury levels and the parameters of reproductive endocrine function (87).

Two reproductive epidemiological studies of male workers occupationally exposed to manganese also yielded contradictory results. Although impotence and lack of sexual desire was higher in the exposed than control group, no significant difference was found in other reproductive outcomes between the groups (89). In another group of workers, which consisted of miners, electric welders in mechanical fields and welders in shipbuilding, a significantly lower sperm count and percentage of total viable sperm was found comparing to control group. However, after adjusting for the influence of copper, nickel, chromium, and iron concentration in semen on the measured reproductive parameters, manganese was no longer a significant predictor of adverse reproductive effects (90).

It was reported that workers exposed to chromium (VI) had significantly higher serum follicle stimulating hormone concentration and lower sperm concentration and motility, seminal plasma zinc levels, lactate dehydrogenase (LDH), and LDH-C<sub>4</sub> (91), and significantly higher

percentage of abnormal sperm than control workers, but other semen quality parameters did not differ between them (92). Blood chromium positively correlated with the percentage of abnormal sperm in the exposed workers (92). While one study of welders exposed to chromium (VI) reported a 67 % decrease in sperm concentration compared to controls and an inverse correlation between sperm concentration and blood chromium levels in the exposed workers (93), another study showed no significant difference in semen quality between welders and other workers (94).

As for boron, there is no clear evidence that occupational exposure impairs sperm concentration, motility, morphology, or DNA integrity (95-97).

No study was found on reproductive effects of occupational exposure to inorganic or organic arsenic in men.

Most of the above-mentioned occupational studies were cross-sectional in design, comparing measured parameters between the exposed and unexposed workers. The most studied metal is lead, whereas only a few occupational reproductive studies were found for mercury, manganese, chromium and boron, and none for arsenic. Some discrepant findings from these studies may be attributed to: different levels and duration of metal exposure, fluctuation in metal exposure levels, no control group or an inadequate control group, a small number of subjects examined, division of subject into categories, lack of relevant

**Table 1** *Reproductive health terminology*

TERM	DEFINITION / EXPLANATION
Spermatogenesis	A cellular process that occurs in seminiferous tubules in the testis and that produces mature male sex cells in ca. 74 days in humans (42); it starts at puberty and usually continues until death.
Endocrine disruptor	An exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that is responsible for the maintenance of homeostasis, reproduction, development and/or behaviour and is able to alter the structure or function of the endocrine system and to cause adverse effects on organisms or their progeny or (sub)populations (57).
Cryptorchidism	Undescended testicle.
Hypospadias	A birth defect of the urethra in the male that involves an abnormally placed urinary meatus (opening), i.e. displacement of the urethral meatus from the tip to the ventral side of the phallus.
Prostate specific antigen (PSA)	A marker that in combination with digital rectal examination is used as an aid in the detection of prostate cancer in men.
Time to pregnancy (TTP)	Time taken to conceive after the couple had stopped using contraceptives and treatment for infertility; The TTP distribution in a population describes its fertility.

information on selection criteria and/or lack of control for other common factors capable of affecting metal concentration and reproductive parameters. Only a few studies were adjusted for age, smoking habits and alcohol consumption (78, 85), and concentration of other metals (78, 90).

#### *Effects of occupational exposure to metals on fertility*

Time to pregnancy (TTP, Table 1) is a frequently used biomarker of effect in occupational epidemiology. Since the unit of study is the couple, information about the potential confounding factors affecting both partners are required.

Several studies (19, 98) have indicated that paternal blood lead levels of approximately  $300 \mu\text{g L}^{-1}$  to  $400 \mu\text{g L}^{-1}$  are the "most likely threshold for increased rate of spontaneous abortions, reduced rate of live births, and prolonged TTP, although inconsistent findings or a minor incompatibility were also reported" (19). A longer TTP was associated with higher blood lead levels within the group of lead workers although shorter TTP was found in lead workers than in controls (98). Seminal plasma lead levels inversely correlated with the fertilising capacity expressed by mannose receptor expression, and fertilisation rate in patients seeking in vitro fertilisation (IVF) (99).

Lauwerys et al. (100) found no effect of occupational exposure to mercury on fertility assessed by the rate of live births, whereas two other studies reported a significant association between paternal occupational exposure to mercury vapour and higher spontaneous abortion rate (101-102).

The results of the only two studies evaluating the influence of paternal exposure to manganese dust on the rate of live births are controversial (100, 103).

Judging by the study of occupational exposure to boron as sodium borate at a large mining and production facility in California (104), paternal exposure does not seem to bear a greater risk for live births.

#### *Effects of environmental exposure to metals on reproductive parameters*

Several studies indicate that adverse reproductive effects of some metals can occur even at an exposure range that is common for general populations worldwide.

Low to moderate lead exposure has been associated with reduced sperm concentration, poor semen motility and viability, and abnormal sperm morphology (66, 105-108). Moreover, blood lead level  $<150 \mu\text{g L}^{-1}$  has been associated with higher serum levels of testosterone and oestradiol, and lower serum levels of prolactin (66). In men with median blood lead of  $15 \mu\text{g L}^{-1}$ , an inverse association with serum prolactin and thyroid stimulating hormone (107) was found, but there was no association between blood lead levels and sperm concentration, motility or morphology (109). A Mexican study in men showed a significant association between lower semen quality and lead in spermatozoa or seminal fluid, but not with blood lead (106). All of these studies have been adjusted for the influence of age and current smoking (66, 105-109), and for other metals (66, 105, 107-109). Other studies (110-114) have not found any association between low-level lead exposure and semen quality or endocrine function in men.

Tobacco smoking significantly increases cadmium levels in blood and seminal plasma in occupationally unexposed men (78, 115-117) and may adversely affect the male reproductive function. Several studies have found evidence that low-level cadmium affects semen quality and/or reproductive hormone levels. The following effects have been reported in men with blood cadmium level  $<1.5 \mu\text{g L}^{-1}$ : decreased sperm density and number of sperm per ejaculate (114), decreased semen volume (114, 118), and increased sperm midpiece defects and immature sperm forms (118). After adjusting for potential confounders, these effects included reduced testis size and higher serum levels of the follicle stimulating hormone, testosterone, and oestradiol (105). In men with median blood cadmium level of  $0.20 \mu\text{g L}^{-1}$ , a positive association between blood cadmium and inhibin B levels in a model adjusted for age, BMI, and current smoking or for other metals (119) was found, but there were no effects on semen parameters (109). Urinary cadmium showed no significant association with serum testosterone, follicle stimulating hormone, and luteinizing hormone levels after adjusting for potential confounders (67).

Several studies (120-122) have indicated that total mercury levels  $>8 \mu\text{g L}^{-1}$  in blood or  $>8 \text{ng L}^{-1}$  in seminal fluid are associated with lower sperm concentration and motility and higher abnormal sperm count. Median total mercury in blood of  $1.10 \mu\text{g L}^{-1}$  has not been associated with parameters of semen quality or endocrine function (109, 123). An increased

risk of subfertility was found to be associated with increasing levels of mercury in hair (124). Consumption of seafood can significantly increase methyl-mercury in blood, hair, and seminal fluid. However, blood methyl-mercury between  $0.11 \mu\text{g L}^{-1}$  and  $16.59 \mu\text{g L}^{-1}$  (median  $2.25 \mu\text{g L}^{-1}$ ) in Swedish fishermen did not affect sperm concentration, count, motility, chromatin integrity, or the proportion of Y-chromosome bearing sperm (125).

Only one group of researchers have evaluated the influence of environmentally relevant levels of manganese on male reproductive ability. They found that blood manganese was significantly associated with low sperm concentration and motility (123, 126), higher inhibin B, and lower prolactin levels (109, 119), although adjusting for confounders produced slightly different results.

The same group of researchers has published results on reproductive toxicity of environmental arsenic in men. Blood arsenic levels higher than  $5.8 \mu\text{g L}^{-1}$  were associated with low sperm motility after adjusting for smoking and age, although the dose response trend was not linear in all groups (109). In a model adjusted for other metals, arsenic was a significant risk factor for low semen volume. In the same group of subjects, blood arsenic increased the risk of low luteinizing hormone level after adjusting for age, BMI, and current smoking (119).

In a study of environmental chromium exposure, seminal chromium levels were not significantly different between fertile and infertile men (127). However, blood chromium was significantly associated with an increase in serum prolactin (107), and a non-linear decrease in serum inhibin B (119) after adjusting for age, BMI, and smoking status, or other metals in both studies.

There is no data regarding the reproductive effects of environmental exposure to boron in men.

With regard to environmental exposure to metals, most information on reproductive effects concern lead, cadmium, and mercury. Some of these studies have been well designed with a sufficient number of participants and appropriately adjusted for potential confounders. However, effects of smoking intensity and alcohol consumption are often not considered, although tobacco smoke and alcohol drinks may be an important source of non-occupational metal exposure. Moreover, smoking and/or alcohol itself may have some detrimental effects on reproductive health in men (128-131).

## REPRODUCTIVE EFFECTS OF EXPOSURE TO METALS AS NANOPARTICLES

Humans have always been exposed to airborne nanoparticles in dust storms, volcanic ash, and other natural processes (132), but this exposure has recently dramatically increased due to the rapid advancement of nanotechnology. Several researchers have expressed concern about the possible adverse effects of nanoparticles on human health because of their ability to pass through biological membranes (132-134) and “translocate through the circulatory, lymphatic, and nervous systems to many tissues and organs” (132). Potential reproductive and developmental toxicity of manufactured nanomaterials was investigated in several experimental *in vivo* and *in vitro* studies reviewed by Ema et al. (135). It was found that “high concentrations of  $\text{TiO}_2$  nanoparticles affect the viability and proliferation of mouse Leydig cells, that gold nanoparticles reduced the motility of human sperm, that silver, aluminium, and molybdenum trioxide were toxic to mouse spermatogonia stem cells, that silica nanoparticles inhibited the differentiation of mouse embryonic stem cells and midbrain cells, respectively, and that cadmium selenium-core quantum dots inhibited pre- and postimplantation development of mouse embryos”. There is no epidemiological study regarding the reproductive effects of nanoparticles.

## CONCLUDING REMARKS

The overall results of this review provide evidence for adverse effects of lead on certain reproductive parameters, and cadmium on prostate impairment and serum testosterone levels, even at moderate to low exposure levels. It seems that mercury and manganese affect semen quality and serum hormone levels, although more studies are needed to confirm these results. Less consistent evidence indicates that arsenic and chromium might adversely affect the male reproductive system, whereas there is no clear evidence that boron exposure might do the same.

Most published studies report the effects of a single metal, although human exposure combines toxic and essential metals that can interact. Influence of other risk factors that can affect metal concentration and/or reproductive parameters in men is rarely considered. No epidemiological study assessing the reproductive

effects of nanoparticles is available. There is insufficient data for establishing quantitative dose-response relationships and no-adverse-effect exposure thresholds for metal-induced reproductive effects in men.

Only a few well-designed epidemiological studies have investigated combined exposure to metals and have been controlled for potential confounders.

Further research evaluating the effects of a particular metal on reproductive health in men should take into account the contribution of other metals, agents, and the lifestyle. A combined analysis could provide useful information about individual health risk.

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**Sažetak****UTJECAJ TOKSIČNOSTI METALA NA REPRODUKCIJSKU FUNKCIJU U MUŠKARACA**

Postoje indikacije da kombinacija genetskih, okolišnih i čimbenika načina života pridonosi uočenom poremećaju reproduktivnog zdravlja u muškaraca. Metali su široko rasprostranjeni u čovjekovu okolišu te u hrani, vodi, zraku, cigaretnom dimu i alkoholnim pićima. Rezultati eksperimentalnih istraživanja sugeriraju štetne učinke većine ispitivanih metala na mušku reproduktivnu funkciju. Međutim, odgovarajuća su istraživanja u ljudi oskudna. Ovaj rad sažima rezultate dosadašnjih epidemioloških istraživanja o učincima izloženosti metalima na mušku reproduktivnu funkciju. Poseban naglasak dan je istraživanjima koja su razmatrala utjecaj istodobne izloženosti različitim metalima uz čimbenike čovjekova načina života i njihovo međudjelovanje na reproduktivne učinke. Objavljeni rezultati daju dovoljno dokaza o štetnom djelovanju olova na neke reproduktivne parametre te kadmija na poremećaj prostate i razinu testosterona u serumu, čak u uvjetima umjerene do niske razine izloženosti. Manje je dokaza o štetnom djelovanju na kvalitetu sjemena i razinu spolnih hormona nađeno za mangan. Podaci koji upućuju na moguće štetno djelovanje žive, arsena ili kroma nisu dosljedni, dok o štetnom djelovanju bora na mušku reproduktivnu funkciju nema jasnih podataka. Utjecaj potencijalno uzročnih varijabli uzet je u obzir samo u nekoliko radova. Stoga buduća istraživanja poremećaja reproduktivnog zdravlja u muškaraca trebaju razmatrati doprinos istovremene izloženosti različitim metalima koji u kombinaciji s ostalim čimbenicima mogu utjecati na osobnu (pre)osjetljivost.

**KLJUČNE RIJEČI:** *kvaliteta sjemena u ljudi, metali, metaloidi, međudjelovanje metala, spolni hormoni*

**CORRESPONDING AUTHOR:**

Alica Pizent  
Institute for Medical Research and Occupational Health  
Ksaverska cesta 2, HR-10000 Zagreb, Croatia  
E-mail: [apizent@imi.hr](mailto:apizent@imi.hr)