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REVIEW ARTICLE **OPEN ACCESS**

Male infertility due to excessive exposure of molybdenum: A mechanistic approach

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ABSTRACT
Molybdenum is considered as an essential microelement which acts as a cofactor for enzymes in the human body as well as regulate various metabolic processes and normal cell functioning. Although molybdenum plays an important role in biological processes, it can cause harmful effects on the metabolism of other trace elements and other vital body organs at high levels. Food and water are the most important source of molybdenum exposure for the general population. Besides this, people may get exposed to molybdenum via inhalation in the areas involved in the mining of Mo ore, or from certain industrial operations. It may also discharge as a pollutant from industrial processes. Various studies in different animal models indicated that high level of molybdenum caused a reduction in the number of germ cells, decline in sperm quality and morphology, decline in testicular and epididymal weight, histopathological and biochemical changes in male reproductive organs. Disturbed gonadal function, disrupted steroid synthetic pathways and generation of reactive oxygen and nitrogen species are enlisted as probable causes of molybdenum-induced male reproductive toxicity. In the present review, we made an effort to sum up the existing data on the adverse effects of molybdenum on the male reproductive function and also emphasize on the potential mechanism of reproductive toxicity induced by molybdenum. The information is retrieved from research articles available on reprotoxic effects of molybdenum.
Keywords: Molybdenum, sperm, reproductive, oxidative stress, histopathology

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INTRODUCTION

For the normal functioning of the body, humans need about 20 essential elements which are required in appropriate amounts. Among them, metals such as Mg, Ca, Fe, Mn, Co, Cu, Zn, Mo are considered as essential elements. Trace metal elements serve a regulative role in spermatogenesis, sperm motility acrosome reaction and secretion of reproductive hormones. Molybdenum is one of the essential metals which serve as a cofactor in various biological reactions in human beings.

Molybdenum (Mo) is the only 4d transition element that is being utilized by biological systems [1]. It is usually found in the body in either the Mo^{4+} or Mo^{6+} valence state bound to sulfur or oxygen. It is essential for the functioning of three important enzymes in the human body: aldehyde oxidase catalyses oxidation of purines, pyrimidines and pteridines; xanthine oxidase catalyses oxidative hydroxylation of purines and pyridines; sulfite oxidase for the conversion of irritating sulfites into harmless sulfates, necessary for metabolism of sulfur amino acids [2, 3]. It has also been reported that molybdenum significantly affects protein synthesis, as well as metabolism of phosphorus, sulphur, potassium, copper, zinc and iodine [4].

MATERIAL AND METHODS

The present review article was prepared through extensive review of available scientific research articles related to molybdenum induced male reproductive toxicity in various animal models. It was tried to gather maximum data from reputed science journals and published reports from various international agencies. Various search engines like Pubmed, Science direct, Scopus and Web of Science were used for literature survey.

MOLYBDENUM IN THE ENVIRONMENT

Mining, milling, smelting operations, coal-fired power plants and coal combustion are the major activities through which molybdenum can release into the environment. Once released to the air, it settled to the ground by gravity. It becomes attached to the organic compounds and other components in the soil or in the water. The soil conditions, especially the acidity of the soil, influence the binding of molybdenum to soil and sediment [5].

EXPOSURE TO MOLYBDENUM

Food is the most important source of Molybdenum exposure. Among foods, Mo is found in leafy vegetables and legumes at higher concentrations [6]. Humans can also get exposed to molybdenum by breathing air, by drinking water, and by skin contact with soil and water. Generally low level (<2 µg/L) of Molybdenum is found in groundwater, but it may reach up to 25 mg/l in groundwater due to increased anthropogenic or industrial activities [7]. The WHO recommends a maximum level of 0.07 mg/l molybdenum in drinking water. Beside this, industrial and occupational exposure can also occur [8].

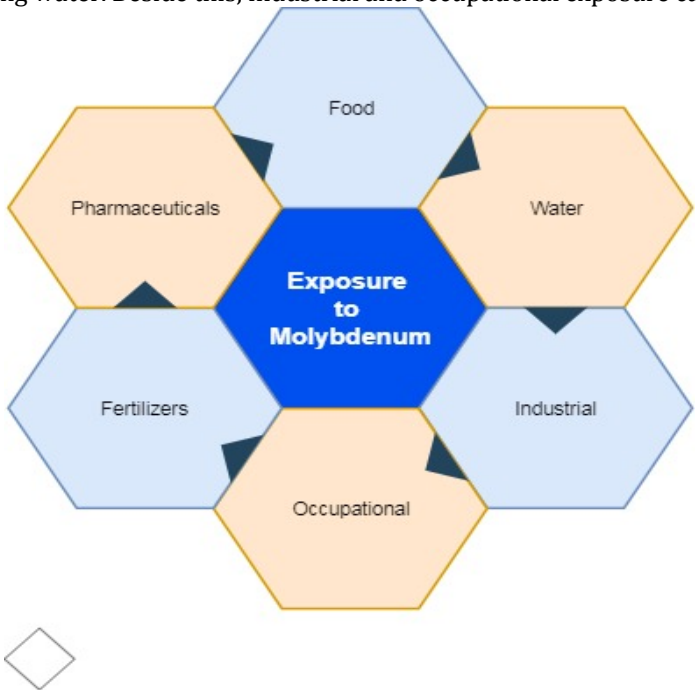

Figure 1 showing various ways through which humans can get exposure to molybedenum

APPLICATIONS OF MOLYBDENUM

Molybdenum is used mainly as an alloying element in steel, cast iron, super alloys and in the electronics industries. It is used in industrial catalysts, corrosion inhibitors, pigments, glass, ceramics, enamels, flame retardant for polyester and polyvinyl chloride resins, as crop nutrients in agriculture, in contact lens solutions, as color additives in cosmetics and as reagents in chemical analyses [9]. A radioactive isotope of molybdenum, 99Mo, is used as a source to produce the metastable radioisotope technetium-99m (99mTc), which is an important radiopharmaceutical that is being used in the vast majority of high resolution medical imaging tests.

Patients with sulfite sensitivity [10]; Wilson's disease [11]; dental caries [12]; malabsorption states [13] and certain type of cancers [14, 11] are being treated with molybdenum supplementation. It has been also recommended as an antidiabetic agent. Molybdate treatment has also shown beneficial effects on antioxidant system and postischaemic cardiac function of diabetic rats [15]. Additionally, it is also present in multi-vitamin and mineral supplements currently at level up to 25µg/day [16].

The biological half-time for molybdenum has been reported to be 42-74 days in slow turnover tissues while 1.7-2.5 days in fast turnover tissues [20]. Oral LD50 value of 1714.3 mg/kg for ammonium molybdate have been reported in laboratory rats [21].

PHARMACOKINETICS

In animals and humans, molybdenum is well absorbed via oral and intravenous routes of absorption. The rate of gastrointestinal absorption of molybdenum depends upon its chemical form, on the route of

exposure and the animal species. Water-soluble and hexavalent molybdenum compounds are readily absorbed when ingested. Gastrointestinal absorption rates of 38 to 77% have been reported for humans and 40-85% for animals [17,18].

Following absorption, molybdenum is transported by the blood to the liver and to the other organs of the body in the molybdate form; it is carried in the blood bound to α-macroglobulin and by adsorption to RBC. The highest molybdenum concentrations are found in the kidneys, liver and bones of most laboratory animals and humans. The presence of dietary copper and sulfate affects the amount of molybdenum absorbed and retained in the body. In laboratory animals, 36–90% of molybdenum is excreted in the urine. As its absorption is usually more rapid than its excretion, the level of Mo in the blood stream may remain high for several days after a single dose and so relatively infrequent dosing will ensure a continual high concentration in the animal [19].

Exposure to molybdenum exerts harmful effects on the vital organ systems of the body like hematopoietic, renal and hepatic system etc. In humans, increased serum urate and gout-like symptoms has also been reported due to excessive exposure of high molybdenum. A few cases of pneumoconiosis have been reported among workers exposed to metallic molybdenum and molybdenum trioxide. Molybdenum poisoning can also cause psychosis with visual and auditory hallucinations, learning disability, major depression, and posttraumatic stress disorder [22]. The Male reproductive system is also one of the important systems being targeted by excessive exposure of molybdenum. Therefore, the aim of the present article is to review available data on the deleterious effects of molybdenum on male reproductive system and also to assess the mechanism involved.

Table 1: Effect of molybdenum exposure on male reproductive system in different animal models

S. No.	Animal model	Dose and duration	Route of administration	Observation	Reference
1.	Bulls	From the 1st to 37th day, the calves were fed 2.6 g.; from 38 to 46 days, 4.0 g.; from 47 to 56 days, 2.8 g.; from 57 to 74 days, 4.0 g.; and from 75 to 129 days, 5.0 g of the $Na_2MoO_4.2H_2O$ daily.	Oral	Lack of libido, marked damage to interstitial cells and germinal epithelium along with little or no spermatogenesis in bulls.	[23]
2.	South African Mutton Merino rams	Control diet (8.02 mg Cu/kg, 1.3 mg Mo/kg and 0.22% S); the molybdenum supplemented diet (3.45 mg Cu/kg, 40.0 mg Mo/kg and 0.22% S); and the molybdenum and sulphate (MS) supplemented diet(3.55 mg Cu/kg, 38 mg Mo/kg and 0.34% S).	Oral	Lower ejaculate volume, lower sperm concentration, poorer sperm motility and morphology and lower Peripheral plasma testosterone concentrations was observed in Group MS than in Groups C or M.	[24]
3.	Rats	Sodium molybdate (30 and 50 mg/kg b.wt./day) for 60 days.	Oral	Degeneration and shrinkage of seminiferous tubules, increased intertubular space and degeneration of interstitial cells in testes accompanied with significant dose dependent decrease in sperm motility and total epididymal sperm count in rats	[25]
4.	Sheep	Ammonium tetrathiomolybdate 3.4 mg/kg b.wt. for three alternate days	Sub cutaneous injection	degenerated seminiferous tubules with marked attenuation of the lining epithelium and diminished spermatogenesis was observed	[4]

5.	Male rats	Ammonium tetrathiomolybdate (0, 1, 4 and 12 mg/kg b. wt. /day for 59–61 days) to	Oral	Significant reduction in epididymal weights, sperm counts, sperm motility, sperm morphologic abnormalities and histopathologic changes in testis and epididymis were noticed only at 12 mg/kg/day dose level	[26]
6.	Rabbits	39 mg Mo/kg dry matter (DM) and 40 mg Mo/kg DM for 14 days.	Fed with commercial pellets and carrots containing Molybdenum	Reduction in the number of germ cells and mature spermatocytes	[27]
7.	Human (Male)	clinical study	**-**	An inverse association was found between Mo concentrations in blood and semen quality.	[28]
8.	Human(Male)	Cross-sectional epidemiological study at Michigan, USA	-	A significant inverse trend was noticed between molybdenum and testosterone in blood.	[29]
9.	Mice (Male)	12.5, 25, 50, 100, 200 mg/L Molybdenum for 14 days	Oral	Sperm parameters, including the epididymis index, sperm motility, sperm count, and morphology were negatively affected	[30]
10	Sprague-Dawley rats (Male)	sodium molybdate dihydrate at dose levels of 0, 5, 17 or 60mgMo/kgbw/day for 90days.	Diet	No adverse effects on reproductive organ weights or histopathology, estrus cycles or sperm parameters were observed at any dose level.	[31]
11.	Wistar Rats (Male)	50, 100 and 150 mg/kg b.wt./day ammonium molybdate for 60 days. Recovery study was also performed by dose withdrawal in highest dose group (150 mg/ kg b.wt./ day) for next 60 days.	Oral	Reduction in serum testosterone, FSH, LH, sperm count, motility and viability. The level of TBARs was increased while the activities of superoxide dismutase and concentration of glutathione and ascorbic acid was decreased	[32]
12.	Wistar Rats (Male)	50, 100 and 150 mg/kg b.wt./day ammonium molybdate for 60 days. Recovery study was also performed by dose withdrawal in highest dose group (150 mg/ kg b.wt./ day) for next 60 days.	Oral	Reduction in the germ cell population as well as diminution in seminiferous tubular diameter, Leydig cell nuclear diameter. Marked degeneration in spermatogenic and Leydig cells.	[33]
13.	Male mice	Group NC fed with Cu-	Oral	Administration of High	[34]

		deficient diet and received 3 mg/L Cu in the drinking water; Cu-deficient diet, was given to the low Cu (LCu) group; 400 mg/LMo in the drinking water, as the high molybdenum (HMo) group; and (4) Cu-deficient diet 3 mg/L Cu and 400 mg/L Mo in the drinking water, as the HMo and low Cu (HMoLCu) group.		Mo, not only decreased sperm density and motility but also increased the rate of teratosperm occurrence. A significant increase in MDA content and a decrease in SOD, GSH-Px, and T-AOC contents were observed. Testicular tissues and cells of mice were damaged by HMo and the damages were more serious in the case of Cu deficiency.	

MECHANISM OF TOXICITY

After review of related published articles, it can be suggested that excessive exposure to molybdenum can lead to testicular or sperm toxic effects by variety of mechanism including imbalance in mineral metabolism, endocrine disruption, oxidative stress etc.

Effects on copper metabolism

Molybdenum has a chelating effect on copper and is associated with impaired copper utilization. High levels of Molybdenum interfere with the absorption and metabolism of Copper in the body. It forms complex with sulfur and copper that makes copper unavailable for uptake. Hypocuprosis due to molybdenum toxicity has been reported in cattle, sheep, rabbits, rats, guinea pigs and poultry [35, 36]. Over supplementation of molybdenum can result in toxic effects on reproductive system which may be directly related to resultant copper deficiencies. Copper deficiency caused by molybdenum exposure may be responsible for the diminished level of FSH and LH [43, 44] which are essential for normal reproductive function. Haywood *et al*., [42] further explicated that reduced copper content make it unavailable for a copper-dependent enzyme peptidylglycine α-amidating mono-oxygenase (PAM) that is crucial for the bioactivation of many peptide hormones, including FSH and LH.

Copper is also necessary for the normal spermatogenesis. It acts as a metal cofactor for numerous enzymes, e.g., diamine oxidase, copper/zinc (Cu/Zn) SOD, cytochrome c oxidase and tyrosinase. These copper-dependent enzymes are required in somatic and germ cells in the testis and epididymis for normal sperm structure and function [37, 38]. A number of human and animal studies have demonstrated that Cu has direct and positive effects on semen quality parameters. A significant decrease in Cu levels has been observed in the seminal plasma of azoospermic male patients in comparison to healthy controls [39]. Furthermore, a significant positive correlation between blood Cu and sperm count has also been observed by Machal *et al*., [40] Wong *et al*., [41]. The copper deficient state created through excessive molybdenum has been found responsible for lower sperm concentration, motility and spermatotoxic effects in rams [24], in rats [25, 26] and in bulls [23].

Endocrine disruption

Endocrine dysfunction is another important mechanism by which molybdenum can cause reproductive toxicity. It can accumulate in hypothalamus, pituitary, adrenal, testis or ovary and can interfere with their endocrine efficiency [4]. Molybdenum adversely affects the hypothalamo–adenohypophyseal axis by interfering with trophic hormone (ACTH, FSH, LH) release. It causes atrophy or degeneration of the adenohypophysis with the loss of trophic cells in the pituitary gland of sheep and lead to the pause of reproductive activity [4]

Molybdenum may alter the function of the endocrine system mainly through agonist and/or antagonist activity of sex steroid receptors. Mo may alter testosterone levels by interacting with steroid receptors. It prevents receptor inactivation or transformation which can cause disturbance in the metabolic fate of the major estrogens including testosterone. Such interruptions in the activity of steroid hormones may cause adverse effects on male reproductive function [45].

Oxidative stress

Molybdenum- induced oxidative stress might be responsible for reprotoxic effects. Increased lipid peroxidation, enhanced production of reactive oxygen species or decreased level of antioxidants due to molybdenum exposure can lead to oxidative stress. [46]

Rats treated with ammonium molybdate exhibited an increase in lipid peroxidation in the testis which could be due to a concomitant increase in the generation of free radicals or reduced content/activity of antioxidants in testis. Reduced level of intratesticular testosterone might also be responsible for suppressing expression of antioxidant enzymes with a concomitant increase in peroxidative damage, disruption of spermatogenesis and an increase in germ cell apoptosis [47].

Oxidative stress may cause dysfunction in sperm motility loss of membrane integrity, increased cell permeability, enzyme inactivation, structural damage of DNA, Seminal plasma contains antioxidant enzymes, such as superoxide dismutase, glutathione peroxidase and catalase and nonenzymatic antioxidants, such as ascorbate or thiol groups. Spermatozoa contain high amount of polyunsaturated fatty acids and a little amount of cytoplasm which makes it extremely susceptible to oxidative attack. So elevated level of reactive oxygen species can made spermatogenic cells more vulnerable resulting in lessen sperm count. [1].

Oxidative stress might be associated with the imbalance of trace metals. Super oxide dismutase requires copper and zinc for its functional activity and stability [47]. Molybdate can induce abnormal metabolism or displacement of metals like Zn and Cu which might be one of the possible reasons of reduced SOD activity. Oxidative stress results in testis due to decreased SOD activity which in turn affects the sperm quality parameters. Zhai *et al.,* [30] have reported that at high doses (≥ 100 mg/L) molybdenum induce negative effects on epididymis index, sperm motility, sperm count and morphology accompanied by changes in the activities of superoxide dismutase and glutathione peroxidase, and the level of malondialdehyde in the testes.

Figure 2. Various mechanisms through which molybdenum cause reproductive toxicity

SUMMARY AND CONCLUSIONS

Molybdenum is an essential trace mineral for many important enzymes in living organisms, but its distorted homeostasis can result in toxicity. On the basis of review, we concluded that male reproductive

system is more sensitive to molybdenum exposure than the female reproductive system. It can lead to male infertility via disturbed steroidogenesis and spermatogenesis. Therefore, appropriate preventive measures and actions should be taken in order to minimize the risk of male infertility problems arising due to excessive exposure of molybdenum.

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