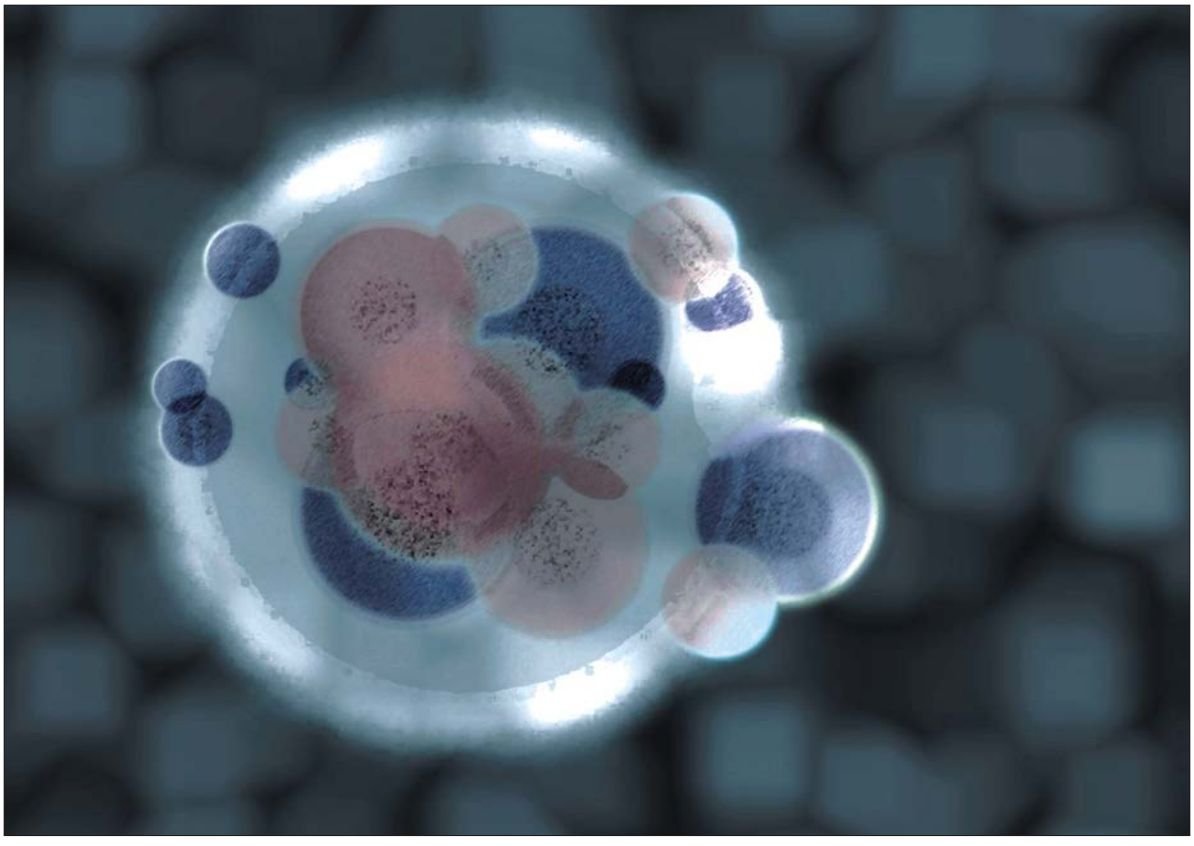

Journal of Biological Sciences

ISSN 1727-3048

science alert

ANSInet
an open access publisher
http://ansinet.com

Journal of Biological Sciences 10 (5): 396-404, 2010
ISSN 1727-3048

Male Reproductive Toxicity of Some Selected Metals: A Review

N. Mathur, G. Pandey and G.C. Jain
Center For Advanced Studies, Department of Zoology,
University of Rajasthan, JLN Marg, Jaipur-302 004, India

Abstract: The management of infertility problems has become an increasingly important part of health services during the past 20 years. A substantial number of couples seek fertility treatment due to poor semen quality and there is evidence in the literature that male reproductive function seems to have deteriorated considerably in the past four-five decades. Exposure to metals is a common phenomenon due to their environmental pervasiveness. Some metals are essential for life, others have unknown biological functions, either favorable or toxic and some others have the potential to caused toxicity. Over exposure of metals are in fact, one of the oldest environmental problems and they are widely distributed in the environmental workplace. One of the major mechanisms behind metal toxicity has been attributed to oxidative stress. A growing amount of data provide evidence that metals are capable of interacting with nuclear proteins and DNA causing oxidative deterioration of biological macromolecules. The primary objective of this review is to highlight the effects of metals on male reproductive processes.

Key words: Infertility, semen quality, metals, oxidative stress

INTRODUCTION

It is undeniable that good quality semen is essential for reproductive success. This quality appears to have been directly affected in recent years. Since 1990s, various authors have reaffirmed that possible significant drop in sperm quality and consequently an increase in male infertility rates (Carlsen *et al*., 1992; Jensen *et al*., 2008; Traina *et al*., 1994). During the past 50 years, tens of thousands of metals, chemicals have been released into the general environment (Carbone *et al*., 2007). Over exposure of these metals cause severe damage in male reproductive health.

The use of metals has been critical to the progress and success of human civilization. It would be difficult to imagine an advanced society without extensive utilization of metallic compounds. Metals are unique among pollutant toxicants in that they are all naturally occurring and in many cases, are ubiquitous within the human environment. In addition, all life has evolved in the presence of metals and organisms have been forced to deal with these potentially toxic, yet omnipresent, elements. In fact, many metals have become essential to various biological processes. Essentiality goes hand-in-hand with intentional accumulation and safe transport, storage and usage mechanisms. Nonetheless, even essential metals will become toxic with increasing exposure. It is often the case that the nonessential toxicant metals mimic essential metals and thereby gain access to and potentially disrupt, key cellular functions. This can also account for bioaccumulation of toxic metals (Veado *et al*., 2006; Kutlubay *et al*., 2007).

Metal toxicity is believed to be mediated through macromolecules such as proteins with structural, catalytic or transport function and DNA. Reactive oxygen species are generated by metals, particularly transition metal ions e.g., of iron, copper, vanadium, cobalt, can overcome the spin restriction of O_2 and donate a single electron, giving rise to free radical species and chain reaction. Toxicity occurs when such metals are free and reactions become uncontrolled. Metals also inhibit protection mechanism against reactive oxygen species, e.g., SOD, glutathione. Other important cytotoxic mechanism for some metals (e.g., mercury and chromate) are DNA damage and inhibition of cellular respiration (e.g., arsenic and chromate). Although, metals can bind to a wide variety of cellular ligands and the effects produced seem to be relatively specific for each metal (Maret and Standstead, 2006; Luebke *et al*., 2006).

The rapid industrialization and overgrowing urbanization, the effects of metals on male reproductive system have become major health concern globally (Chowdhury, 2009; Turgut *et al*., 2003). This study we reviewed metals that have been reported to produce significant toxicity in male reproductive system.

Effect of various metals on male reproduction is presented in Table 1.

Corresponding Author: Gyan Chand Jain, Department of Zoology, University of Rajasthan, Jaipur-302 004, India

Table 1: Effect of various metals on male reproduction

Metal	Animal	Route administration	Duration	Dose	Observations	Reference
Aluminum chloride	New Zealand white rabbit	Orally	16 weeks	34 mg/kg/alternate day	Dead and abnormal sperm were increased. Body weight, feed intake and relative weights of testes and epididymis were decreased. Concentration of thiobarbituric acid-reactive substances (TBARS) were increased in seminal plasma	Yousef *et al.* (2005)
Aluminum chloride	Mouse	Drinking water	12 weeks	1000, 1200 and 1400 ppm day^{-1}	Reduction of fertility and an increase in the number of resorbtions. The testicular spermatid and epididymal sperm counts were reduced .There was an increase in the levels of testosterone and LH in serum	Mayyas *et al.* (2005)
Aluminum chloride	Mouse	Intraperitoneal injection	14 days	0, 13, or 35 mg Al/kg b.wt./day	High concentration of aluminium in human spermatozoa and seminal plasma correlates with decreased sperm motility and viability	Guo *et al.* (2002)
Sodium arsenite	Mouse	Drinking water	365 days	4 ppm day^{-1}	Decrease in the absolute and relative testicular weight but epididymal and accessory sex organ weights were similar to control. Sorbitol dehydrogenase, acid phosphatase and 17β-hydroxysteroid dehydrogenase (17β-HSD) were decreased, but those of lactate dehydrogenase and γ-glutamyl transpeptidase (γ-GT) were increased in testis	Pant *et al.* (2004)
Arsenic tri oxide	Rat	Orally	28 days.	3 mg /kg b.wt./day	Increase in seminiferous tubular luminal size coupled with reduced accumulation of spermatozoa and signs of necrotic changes with disarray in cellular organization. Decrease in sperm count, viability and motility	Mnkherjee and Mnkhopadhyay (2009)
Sodium arsenite	Mouse	Drinking water	35 days	53.39, 133.47, 266.95 and 533.90 μmol L^{-1}	A decrease in the activity of 17 β- HSD along with increase in LDH, γGT activity were observed	Pant *et al.* (2001)
Sodium-meta-arsenite	Mouse	Drinking water	30, 45 and 60 days	30 and 40 mg L^{-1}	Decrease in the relative testicular weight. Reductions in seminiferous tubular diameter and various gametogenic cell population. Leydig cell atrophy was significantly increased in dose dependent manner	Sarkar *et al.* (2003)
Sodium arsenite	Mouse	Intraperitoneal injection	2 days	10 mg kg^{-1} b.wt.	Degeneration of the seminiferous tubules with necrosis and defoliation of spermatocytes. Decreased the activities of the antioxidant enzymes, as well as the levels of cellular metabolites. Enhanced testicular arsenic content, lipid peroxidation, protein carbonylation and the level of glutathione disulfide (GSSG)	Manna *et al.* (2008)
Gallium arsenide	Rat	Intratracheal instillation	Single	7.7 mg kg^{-1}	A decrease in sperm count and increase in the proportion of morphologically abnormal sperm in the epididymis. There was 40-fold increase in the degenerating late elongated spermatids at the postspermiation stages, stages IX, XI and XI	Omura *et al.* (1996)
Arsenic	Human	Occupational			Sperm abnormalities occur.	Golub (1992)
Arsenic	Human	Occupational			Decrease serum testosterone and prostate cancer occurs	Benbrahim-Tallaa and Waalkes (2008)
Cadmium chloride monohydrate	Sprague-Dawley rat	Drinking water	30 days	15 ppm	Damaged the seminiferous tubules and caused the degeneration and disintegration of spermatogenic cells. Leydig cells were also lost after cadmium treatment	Dilek and Cengiz (2008)
Cadmium chloride	Rat	Subcutaneous injection	Single	3 mg Cd kg^{-1} b.wt.	Decrease in sperm count and motility. LPO increased in testes	Ono *et al.* (1997)
Cadmium chloride	Rat	Orally	5 weeks	20 mmol $CdCl_2$ kg^{-1} b.wt.	LH and testosterone level decreased in serum	Waalkes *et al.* (1997)
Cadmium	Sprague-Dawley rat	Intraperitoneal	5 weeks	1, 2, 4 or 8 mg kg^{-1} b.wt.	The spermatids and dead Sertoli cells increased in the seminiferous tubules while interstitial cells decreased and inflammatory cells increased in the interstitial tissues	Yang *et al.* (2006)
Cadmium chloride	Mouse	Intraperitoneal	Single	2.5 or 5 mg kg^{-1} b.wt.	Inhibition of catalase and SOD activities, reduction in ascorbic acid, increase of lipid	Santos *et al.* (2004)

Table 1: Continued

Metal	Animal	Route administration	Duration	Dose	Observations	Reference
					peroxidation induced by cadmium, indicating testes damage	
Cadmium chloride	Mouse	Drinking water	45 days	0, 23 and 50 mg kg^{-1} b.wt.	The sperm count, sperm motility, sperm maturity and the level of testosterone decreased in the high dose administered group. Histological studies showed a severe necrosis and atrophy in the testis of high dose group, consequently, there was no successful mating in some groups. The number of newborns, their weights and crown rump lengths reduced	Monsefi *et al.* (2009)
Cadmium chloride	Rat	Orally	30 days	40 mg L^{-1}	Reduction in growth rate and relative weights of testes and seminal vesicles. Treated rats displayed a decrease in testicular and plasma testosterone levels, epididymal sperm count and spermatozoa motility	Amara *et al.* (2008)
Cadmium	Human	Occupational			Testicular necrosis	Ragan and Mast (1990)
Cadmium	Human	Occupational			Reduction in sperm count and serum testosterone	Siu *et al.* (2009)
Chromic acid	Mouse	Intraperitoneal	Single	1 mg kg^{-1} b.wt.	Chromium-induced reactive oxygen species (ROS) in testes or alter sperm morphology. Suppressed antioxidant enzymes and ascorbic acid. Increase in the level of LPO	Acharya *et al.* (2006)
Potassium dichromate	New Zealand white rabbit	Oral gavage	10 weeks	3.6 mg and 5 mg kg^{-1}	Testosterone levels, body weight, relative weights of testes and epididymis all decreased. Levels of thiobarbituric acid reactive substances increased, whereas the activities of glutathione S-transferase, transaminases and phosphatases decreased in the seminal plasma	Yousef *et al.* (2006)
Potassium dichromate	Monkey (*Macaca radiata*)	Drinking water	6 months	50, 100, 200 and 400 ppm	Decreased sperm count, sperm forward motility and the specific activities of antioxidant enzymes, superoxide dismutase, catalase and the concentration of reduced glutathione in both seminal plasma and sperm	Subramanian *et al.* (2006)
Potassium dichromate	Mouse	Drinking water	12 weeks	150 ppm	Reduced body weight gain. Histological examination showed that chromium exposure induced severe pathologic changes in testis	Afonne *et al.* (2002)
Hexavalent chromium	Non-human primate (*Macaca radiata Geoffroy*)	Drinking water	6 months	100, 200, 400 ppm	Disrupts spermatogenesis by inducing free radical toxicity and supplementation of antioxidant vitamins may be beneficial to the affected subjects	Aruldhas *et al.* (2005)
Hexavalent chromium	Human (workers)	Occupational			Damage in seminiferous tubules epithelium, reduction of spermatozoa formation and increase in prevalence of teratospermia in exposed workers	Li *et al.* (1999)
Cobalt chloride	Mouse	drinking water	12 week	200, 400, 800 ppm	Hypertrophy of the interstitial Leydig cells, congested blood vessel and degeneration of spermatogonial cells and necrosis of both the seminiferous tubules and the interstitial tissues	Elbetieha *et al.* (2008)
Cobalt chloride	Hamster	Intraperitoneal	Single	20, 10, 5 mg $CoCl_2$ kg^{-1} b.wt.	Volume of seminiferous epithelium was decreased and the relative volume of interstitium was increased	Lnkac *et al.* (2007)
Lead acetate	Wistar rat	Drinking water	30 days	7 mg dL^{-1}	Serum testosterone, sperm concentration and production rate were significantly suppressed	Sokol and Berman (1991)
Lead nitrate (PbNO3)	Rat	Intraperitoneal	Single	50, 25 and 12.5 mg kg^{-1} b.wt.	Increased incidence of apoptosis in the spermatogenetic cells and occurrence of empty spaces as well as with the higher apoptosis incidence in germinal epithelium	Massanyi *et al.* (2007a)
Lead acetate	Rat	Oral gavage	90 days	250 and 500 mg L^{-1}	Reduction of epididymal and testicular sperm counts including daily sperm production	Hamadouche *et al.* (2009)
Lead chloride	Mouse	Subcutaneous injection	4 days	74 and 100 mg Lead chloride/kg b.wt.	Epididymal sperm density, motility, viability, mitochondrial function and acrosome integrity were decreased	Oliveira *et al.* (2009)
Lead acetate	Mouse	Intraperitoneal	Single	100 mg lead	Increase in the number of sperm with abnormal	Acharya *et al.* (2003)

Table 1: Continued

Metal	Animal	Route administration	Duration	Dose	Observations	Reference
				acetate/kg b.wt.	morphology and a decrease in sperm counts	
Lead acetate	Rat	Intraperitoneal	Once a week, for 6 and 9 weeks	10 mg lead acetate/kg b.wt.	Decrease in sperm count and sperm motility in cauda epididymis	Hsu *et al.* (1997)
Lead	Human	Occupational			Decrease germ cell population in testes related to an apoptotic process	Martynowicz *et al.* (2005)
Lead	Human	Occupational			Sperm abnormalities	Telisman *et al.* (2007)
Lithium carbonate	Rat	Diet	90 days	800, 1100 mg/kg diet/day	Lithium carbonate (1100 mg kg^{-1}) caused degeneration of spermatogenic cells and vacuolization of sertoli cells cytoplasm in the testis. The serum testosterone level was reduced. Seminal vesicle and prostate secretions were completely blocked and spermatozoa were not seen in the lumen of epididymis and vas deferens	Thakur *et al.* (2003)
Lithium chloride	Rat	Intraperitoneal injection	35 days	1 mmol/kg b.w./day	Degenerative changes in the seminiferous tubules, absence of spermatozoa in the testis, epididymis and vas deferens and absence of secretions in the lumen of seminal vesicle and prostate	Perez Romera *et al.* (2000)
Lithium carbonate	Rat	_____	21 days	35 mg/kg b.wt./day	Early stages of spermatogenic cells showed nuclear protrusions and swellings because of an extensive enlargement of the outer nuclear membrane	Zarnescu and Zamfirescu (2006)
Manganese	Mouse	Oral	43 days	7.5, 15.0 and 30.0 mg/kg/day	Decrease in sperm motility and sperm counts. There were no alterations in the fertility or histology of the testes when compared with the controls	Pounapakkam *et al.* (2003)
Manganese (Mn_3O_4)	Rat	Diet	224 days	350, 1050, 3500 ppm	Fertility and serum testosterone level were reduced.	Laskey *et al.* (1985)
Manganese chloride	Rat	Intraperitoneal injection	2, 4, 24, 48 h	0.01, 0.1, 1.0 mM	Dose and time-dependent reductions of human chorionic gonadotropin (hCG)-stimulated testosterone level	Cheng *et al.* (2003)
Mercuric chloride	Mouse	Oral		0.00, 0.25, 0.50 and 1.00 mg/kg b.wt./day	Fertility and litter size were reduced.	Khan *et al.* (2004)
Mercuric chloride	Mouse	Oral	45 days	1.25 mg/kg/day	Reduction in epididymal sperm count, sperm motility and sperm viability.	Rao and Sharma (2001)
Mercuric chloride	Mouse	Drinking water	12 weeks	4 ppm	Decreased the absolute and relative testicular weights and epididymal sperm number and histological study showed remarkable degenerative lesions in testes	Orisakwe *et al.* (2001)
Mercuric chloride	Rat	Intraperitoneal injection	Single	5, 10 and 20 mg/kg/day	In testis undulation of basal membrane, dilatation of blood vessels in interstitium and occurrence of empty spaces in germinal epithelium were observed. Decreased relative volume of germinal epithelium, increased relative volume of interstitium and increased apoptosis occurrence suggest damaged interstitium and revealed occurrence of edemas. The relative volume of seminiferous tubules showed higher luminization. The number of nuclei was decreased in all experimental groups what is in positive relation with occurrence of empty spaces	Massanyi *et al.* (2007b)
Mercuric chloride	Rabbit	Diet	3 weeks	1 gm kg^{-1} food	Decrease in sperm speed, motility and viability. The histological profile showed a cellular necrosis, accompanied by the absence of spermatozoa in the seminiferous tubes and an increase in interstitial space	Yasmina and Abdennour (2008)
Mercuric chloride	Rat	Drinking water	90 days	0, 50 and 100 ppm	Qualitative examination of testicular sections revealed a fewer mature luminal spermatozoa in comparison to the control. Decline of the reproductive performance of male rats. Loss of antioxidant defense system in testes	Boujbiha *et al.* (2009)
Methyl murcury	Human	Occupational			Sperm viability, sperm motility and sperm count decreased.	Rignell-Hydbom *et al.* (2007)

Table 1: Continued

Metal	Animal	Route administration	Duration	Dose	Observations	Reference
Mercury	Human	Diet (sea food)			Infertile male with abnormal semen	Choy *et al.* (2003)
Ammonium molybdate	Rat	Orally	60 days	10, 30 and 50 mg kg b.wt.	Degeneration of testicular morphology and function and dose dependent decline of the concentration, motility and normal morphology of spermatozoa	Pandey and Singh (2002)
Molybdenum (Na_2Mo_4)	Bull	Orally	129 days	2.6 g animal^{-1}	Reductions in seminiferous tubular diameter. Degeneration of Sertoli cells, germ cells and lumen devoid of sperm	Thomas and Moos (1951)
Molybdenum	Human	Occupational			Decreased in serum testosterone level	Meeker *et al.* (2008)
Nickel sulphate	Mouse	Orally	35 days	5 and 10 mg kg^{-1}	The sperm abnormality, associated with decrease In sperm motility and sperm count was observed. Alterations in the activities of marker testicular enzymes, viz. sorbitol dehydrogenase (decrease), lactate dehydrogenase (increase) and -glutamyl transpeptidase (increase)	Pandey *et al.* (1999)
Nickel chloride	Mouse	Intraperitoneal injection	3 days	1.25, 2.5 and 5.0 mmol/100 g of b.wt./day	Increased LPO in testis. Apoptosis occurs in testis	Doreswamy *et al.* (2004)
Nickel chloride	Mouse	Intraperitoneal injection	Single	20 mg $NiCl_2$/kg body mass	Decrease of germinal epithelium and increase in the relative volume of the interstitium. The diameter of the seminiferous tubule was markedly decreased	Massanyi *et al.* (2007c)
Nickel sulfate	Rat	Intraperitoneal injection	10 doses for alternate days	2.0 mg/100 g b.wt.	Testicular glycogen and cholesterol were increased but total protein concentration decreased in nickel treated rats	Das and Dasgupta (1997, 2002)
Nickel sulfate	Mouse	Orally in distilled water	35 days	5, 10 or 20 mg kg^{-1} b.wt./day	Epididymal sperm count and motility decreased and numbers of abnormal sperm were increased in dose dependently	Pandey and Srivastava (2000)
Nickel subsulfide	Rat	Intratesticular injections	Acute	0.6 to 10 mg	Necrosis of seminiferous tubules and interstitial cells resulting an atrophic changes in testes	Damjanov *et al.* (1978)
Nickel chloride	Rat	Drinking water	28 or 42 days	10-100 ppm	Shrinkage of the seminiferous tubules and decrease in the number of basal spermatogonia	Kakela *et al.* (1999) Waltschewa *et al.*
Nickel sulfate	Rat	Orally	120 days	25 mg kg^{-1} b.wt.	Degeneration of testicular germinal epithelium and interruption of spermiogenesis	(1972)
Nickel sulfate	Rat	Dermal exposure	15 and 30 days	0, 40, 60 and 100 mg Ni/kg b.wt.	Degenerated sperms and edematous fluid were observed in the testis	Mathur *et al.* (1977)
Nickel	Human (Indian welders)	Occupational			A significant positive correlation between the percentage of tail defects in spermatozoa and blood nickel concentration was observed in workers	Danadevi *et al.* (2003)
Nickel	Human (Indian welders)	Occupational			Sperm abnormalities occur	Slivkova *et al.* (2009)
Selenium	Rat	In diet	6 and 9 weeks	6 and 8 ppm	Reduction in body and reproductive organ weights but increase in number of morphologically abnormal spermatozoa. Dose-time-dependent reduction in tubular diameter, epithelial height, number of spermatogenic cells and disintegration of cellular associations in the seminiferous tubules of testes along with reduction in the diameter of cauda epididymal tubules and pseudostratification of their epithelial lining	Kaur and Kaur (2000)
Selenium	House rat	Ingestion in the diet	5 weeks	2 and 4 ppm	Reduction in its body weight, testicular and cauda epididymidis weights, concentration, motility and percentage of live spermatozoa with a simultaneous increase in the percentage of their abnormal forms	Kaur and Parshad (1994)
Cis-platinum	Rat	Intraperitoneal injection	9 weeks	0.5 mg kg^{-1} b.wt./day	Circulating and intratesticular levels of testosterone and LH declined with no effect on FSH	Seethalakshmi *et al.* (1992)
Platinum complex	Rat	Oral gavage	4 weeks	10 mg/kg/day	Testicular enlargement and degeneration/atrophy of the seminiferous epithelium, formation of multinucleated giant cells and vacuolar degeneration of sertoli cells were also seen	Misawa *et al.* (2000)

Table 1: Continued

Metal	Animal	Route administration	Duration	Dose	Observations	Reference
Tributyltin chloride	Rat	Diet	2-generation	5, 25 and 125 ppm	The weights of the testis and epididymis were decreased and sperm count and viability were reduced in epididymis	Omura *et al.* (2001)
Tributyltin	Mouse	Oral gavage	4 week	0.4, 2.0 or 10 mg kg^{-1} b.wt.	Sperm count decreased in testes. Vacuolization Of Sertoli cells in several seminiferous tubules occurs	Kumasaka *et al.* (2002)
Tributyltin	Mouse	Oral gavage	Single	25, 50, or 100 mg kg^{-1} b.wt.	The number of apoptotic germ cells found inside the tubules was increased. Inhibition of steroidogenesis	Kim and Kim (2008)
Vanadium tetraoxide	Mouse	Oral gavage	60 days	9.4 and 18.8 mg kg^{-1}	Degenerative changes in the seminiferous tubules occur and testosterone level was reduced	Aragon *et al.* (2005)
Vanadyl sulphate	Rat	Orally	60 days	100 mg/kg/day	Degeneration of testicular morphology and function and reduced sperm counts and absolute concentration of motile sperms	Jain *et al.* (2007)

CONCLUSIONS

Increased distribution of metals and metal compounds in the environment, especially through anthropogenic activities, raises increasing concern for ecotoxicological effects. The precise chemical basis of metal toxicology is inadequately understood but a uniform mechanism for all toxic metals is implausible because of the great variation in chemical properties and toxic endpoints. Chemically, metals in their ionic form can be very reactive and can interact with biological systems in a large variety of ways. In this regard, a cell presents numerous potential metal-binding ligands. Such adventitious binding is an important chemical mechanism by which exogenous metals exert toxic effects that can result in steric re-arrangement that impairs the function of biomolecules (Kasprzak, 2002; Kasprzak *et al*., 2003).

Metals may operate through hormonal or genotoxic pathways to affect male reproduction. Metals may penetrate the blood testis barrier to potentially affect spermatogenesis, either by affecting genetic integrity or hormone production. Effects may be at different stages of the cell cycle such as during meiotic disjunction and such abnormalities can have deleterious effects on reproduction and offspring. Exposure to metals has been long associated with low sperm motility and density, increased morphological anomalies and male infertility.

The conclusion of present review revealed that the toxic effects of different metals depend on dose, duration, route of administration in male human and various animal species.

ACKNOWLEDGMENTS

We are greatly indebted to Professor Reena Mathur for providing facilities. The authors are also thankful to the Center for Advanced Studies, Department of Zoology, University of Rajasthan, Jaipur. Ms. Nidhi Mathur is thankful to University Grants Commission, India for providing Research Fellowship.

REFERENCES

Acharya, U.R., R.M. Rathmore and M. Mishra, 2003. Role of vitamin C on lead acetate induced spermatogenesis in Swiss mice. Environ. Toxicol. Pharmacol., 13: 9-14.

Acharya, U.R., M. Mishra, R.R. Tripathy and I. Mishra, 2006. Testicular dysfunction and antioxidative defense system of *Swiss mice* after chromic acid exposure. Reprod. Toxicol., 22: 87-91.

Afonne, O.J., O.E. Orisakwa, O.A. Ekanem and D.D. Akumka, 2002. Zinc protects chromium-induced testicular injury in mice. Indian J. Pharmacol., 34: 26-31.

Amara, S., H. Abdelmelek, C. Garrel, P. Guiraud and T. Douki *et al*., 2008. Preventive effect of zinc against cadmium-induced oxidative stress in the rat testis. J. Reprod. Dev., 54: 129-134.

Aragon, M.A., M.E. Ayala and T.I. Fortoul *et al*., 2005. Vanadium induced ultrastructural changes and apoptosis in male germ cells. Reprod. Toxicol., 20: 127-134.

Aruldhas, M.M., S. Subramanian, P. Sekar, G. Vengatesh, G. Chandrahasan, P. Govindarajulu and M.A. Akbarsha, 2005. Chronic chromium exposure-induced changes in testicular histoarchitecture are associated with oxidative stress: Study in a non-human primate (Macaca radiata Geoffroy). Hum. Reprod., 20: 2801-2813.

Benbrahim-Tallaa, L. and M.P. Waalkes, 2008. Inorganic arsenic and human prostate cancer. Environ Health Perspect., 116: 158-164.

Boujbiha, M.A., K. Hamden, F. Guermazi, A. Bouslama, A. Omezzine, A. Kammoun and A. El-Feki, 2009. Testicular toxicity in mercuric chloride treated rats: Association with oxidative stress. Reprod. Toxicol., 28: 81-89.

Carbone, P., F. Giordano, F. Nori, A. Mantovani and D. Taruscio, 2007. The possible role of endocrine disrupting chemicals in the aetiology of cryptorchidism and hypospadias: A population-based case control study in ruralsicily. Int. J. Androl., 30: 3-13.

Carlsen, E., A. Giwercman, N. Keiding and N.E. Skakkebaek, 1992. Evidence for decreasing quality of semen during past 50 years. Br. Med. J., 305: 609-613.

Cheng, J., J.L. Fu and Z.C. Zhou, 2003. The inhibitory effects of manganese on steroidogenesis in rat primary Leydig cells by disrupting steroidogenic acute regulatory (StAR) protein expression. Toxicology, 187: 139-148.

Chowdhury, A.R., 2009. Recent advances in heavy metals induced effect on male reproductive function-A retrospective. Al Ameen J. Med. Sci., 2: 37-42.

Choy, C.M.Y., C.W.K. Lam, L.T.F. Cheung, C.M. Briton-Jones, L.P. Cheung and C.J. Haines, 2003. Infertility, blood mercury concentrations and dietary seafood consumption: A case-control study. Obstet. Gynecol. Surv., 58: 325-326.

Damjanov, I., F.W. Sunderman, J.M. Mitchell and P.R. Allpass, 1978. Induction of testicular sarcoma in Fischer rats by intratesticular injection of nickel subsulfide. Cancer Res., 38: 268-276.

Danadevi, K., R. Rozati, P.P. Reddy and P. Grover, 2003. Semen quality of Indian welders occupationally exposed to nickel and chromium. Reprod. Toxicol., 7: 451-456.

Das, K.K. and S. Dasgupta, 1997. Alteration of testicular biochemistry during protein restriction in nickel treated rats. Biol. Trace Element Res., 60: 243-249.

Das, K.K. and S. Dasgupta, 2002. Effect of nickel sulfate on testicular steroidogenesis in rats during protein restriction. Environ. Health Perspect., 110: 923-926.

Dilek, B. and B. Cengiz, 2008. Protective effects of zinc on testes of cadmium-treated rats. Bull. Environ. Contam. Toxicol., 81: 521-524.

Doreswamy, K., B. Shrilath, T. Rajeshkumar and Muralidhara, 2004. Nickel-induced oxidative stress in testis of mice: evidence of DNA damage and genotoxic effects. J. Androl., 25: 996-1003.

Elbetieha, A., A.S. Al-Tthami, R.K. Al-Thami, H. Darmani and W. Owais, 2008. Effect of chronic exposure to cobalt chloride on the fertility and testes in mice. J. Applied Biol. Sci., 2: 1-6.

Golub, M.S., 1992. Reproductive toxicology of water contaminants detected by routine water quality testing. Epidemiology, 3: 125-129.

Guo, C.H., H. Chang-Jen, C. Ya-Ling and H. Guoo-Shyng, 2002. Low-dose mercury induces testicular damage protected by zinc in mice. Biol. Trace Element Res., 86: 145-157.

Hamadouche, N.A., M. Slimani, B. Merad-Boudia and C. Zaoui, 2009. Reproductive toxicity of lead acetate in adult male rats. Am. J. Sci. Res., 3: 38-50.

Hsu, P.C., M.Y. Liu, C.C. Hsu, L.Y. Chen and G.Y. Leon, 1997. Lead exposure causes generation of reactive oxygen species and functional impairment in rat sperm. Toxicology, 122: 133-143.

Jain, G.C., H. Pareek, S. Sharma, M. Bhardwaj and B.S. Khajja, 2007. Reproductive toxicity of vanadyle sulphate in male rats. J. Health Sci., 53: 137-141.

Jensen, T.K., T. Sobotka, M.A. Hansen, A.T. Pedersen, W. Lutz and N.E. Skakkebaek, 2008. Declining trends in conception rates in recent birth cohorts of native Danish women: A possible role of deteriorating male reproductive health. Int. J. Androl., 31: 81-92.

Kakela, R., A. Kakela and H. Hyvarinen, 1999. Effects of nickel chloride on reproduction of the rat and possible antagonistic role of selenium. Comp. Biochem. Physiol. C Pharmacol. Toxicol. Endocrinol., 123: 27-37.

Kasprzak, K.S., 2002. Oxidative DNA and protein damage in metal-induced toxicity and carcinogenesis. Free Radic. Biol. Med., 32: 958-967.

Kasprzak, K.S., F.W. Sunderman and K. Salnikow, 2003. Nickel carcinogenesis. Mutat. Res., 533: 67-97.

Kaur, R. and V.R. Parshad, 1994. Effects of dietary selenium on differentiation, morphology and functions of spermatozoa of the house rat, *Rattus rattus* L. Mutat. Res., 309: 29-35.

Kaur, R. and K. Kaur, 2000. Effects of dietary selenium (SE) on morphology of testis and cauda epididymis in rats. Indian J. Physiol. Pharmacol., 44: 265-272.

Khan, A.T., A. Atkinson, T.C. Graham, S.J. Thompson, S. Ali and K.F. Shireen, 2004. Effects of inorganic mercury on reproductive performance of mice. Food Chem Toxicol., 42: 571-577.

Kim, S.K. and J.H. Kim, 2008. Inhibitory Effect of tributyltin on expression of steroidogenic enzymes in mouse testis. Int. J. Toxicol., 27: 175-182.

Kumasaka, K., M. Miyazawa, T. Fujimaki, H. Tao and B.R. Ramaswamy *et al*., 2002. Toxicity of the tributyltin compound on the testis in premature mice. J. Reprod. Dev., 48: 591-597.

Kutlubay, R., E.O. Oguz, B. Can, M.C. Guven, Z. Sinik and O.L. Tuncay, 2007. Vitamin E protection from testicular damage caused by intraperitoneal aluminium. Int. J. Toxicol., 26: 297-306.

Laskey, J.W., G.L. Rehnberg, F.J. Hein and S.C. Laws, 1985. Assessment of the male reproductive system in the preweanling rat following Mn3O4 exposure. J. Toxicol. Environ. Health, 15: 339-350.

Li, H., Q. Chen, S. Li, Y. Xu, W. Yao and C. Chen, 1999. Studies on male reproductive toxicity caused by hexavalent chromium. Zhonghua Yu Fang Yi Xue Za Zhi., 33: 351-353.

Luebke, R.W., D.H. Chen, R. Dietert, Y. Yang, M. King and M.I. Luster, 2006. The comparative immunotoxicity of five selected compounds following developmental or adult exposure. J. Toxicol. Environ. Health Part B, 9: 1-26.

Lukac, N., P. Massanyi, M. Zakrzewski, R. Toman, V. Cigankova and R. Stawarz, 2007. Cobalt-induced alterations in hamster testes *in vivo*. J. Environ. Sci. Health A Tox. Hazard. Subst. Environ. Eng., 42: 389-392.

Manna, P., M. Sinha and P.C. Sil, 2008. Protection of arsenic-induced testicular oxidative stress by arjunolic acid. Redox Rep., 13: 67-77.

Maret, W. and H. Sandstead, 2006.. Zinc requirements and the risks and benefits of zinc supplementation. J. Trace. Elem. Med. Biol., 20: 3-18.

Martynowicz, H., R. Andrzejak and M. Medras, 2005. The influence of lead on testis function. Med. Pr., 56: 495-500.

Massanyi, P., N. Lukaa, J. Zemanova, A.V. Makarevich and P. Chrenek *et al*., 2007a. Effect of nickel administration *in vivo* on the testicular structure in male mice. Acta Vet. Brno., 76: 223-229.

Massanyi, P., N. Lukac, A.V. Makarevich, P. Chrenek and Z. Forgacs *et al*., 2007b. Lead-induced alterations in rat kidneys and testes *in vivo*. J. Toxicol. Environ. Health., 42: 671-676.

Massanyi, P., N. Lukac, J. Slivkova, J. Kovacik and A.V. Makarevich *et al*., 2007c. Mercury-induced alterations in rat kidneys and testes *in vivo*. J. Environ. Sci. Health, 42: 865-870.

Mathur, A.K., S.V. Chandra, J. Behari and S.K. Tandon, 1977. Biochemical and morphological changes in some organs of rats in nickel intoxication. Arch. Toxicol., 37: 159-164.

Mayyas, I., A. Elbetieha and W.A. Khamas, 2005. Evaluation of reproductive and fertility toxic potential of aluminium chloride on adult male mice. J. Anim. Vet. Adv., 4: 224-233.

Meeker, J.D., M.G. Rossano, B. Protas, M.P. Diamond and E. Puscheck *et al*.,` 2008. Cadmium, lead and other metals in relation to semen quality: Human evidence for molybdenum as a male reproductive toxicant. Environ. Health Perspect., 116: 1473-1479.

Misawa, Y., K. Watanabe, T. Sakurai, E. Fujii, K. Tsukamoto, A. Kato and T. Sugimoto, 2000. Collaborative work to evaluate toxicity on male reproductive organs by repeated dose studies in rats. Testicular toxicity of 2- or 4-week repeated or single-dose administration of a novel platinum complex. J. Toxicol. Sci., 25: 117-127.

Monsefi, M., S. Alaee, A. Moradshahi and L. Rohani, 2009. Cadmium-induced infertility in male mice. Environ. Toxicol., 25: 94-102.

Mukherjee, S. and P.K. Mukhopadhyay, 2009. Studies on arsenic toxicity in male rat gonads and its protection by high dietary protein supplementation. Al Ameen J. Med. Sci., 2: 73-77.

Oliveira, H., M. Spano, C. Santos and M. de Lourdes Pereira, 2009. Lead chloride affects sperm motility and acrosome reaction in mice: Lead affects mice sperm motility and acrosome reaction. Cell Biol. Toxicol., 25: 341-353.

Omura, M., A. Tanaka, M. Hirata, M. Zhao and Y. Makita *et al*., 1996. Testicular toxicity of gallium arsenide, indium arsenide and arsenic oxide in rats by repetitive intratracheal instillation. Fundam. Appl. Toxicol., 32: 72-78.

Omura, M., R. Ogata, K. Kubo, Y. Shimasaki and S. Aou *et al*., 2001. Two-generation reproductive toxicity study of tributyltin chloride in male rats. Toxicol. Sci., 64: 224-232.

Ono, H., T. Funakoshi, H. Shimada and S. Kojima, 1997. Comparative effect of disulfiram and diethyldithiocarbamate against testicular toxicity in rats caused by acute exposure to cadmium. J. Toxicol. Environ. Health, 50: 389-400.

Orisakwe, O.E., O.J. Afonne, E. Nwobodo, L. Asomugha and C.E. Dioka, 2001. Low-dose mercury induces testicular damage protected by zinc in mice. Eur. J. Obstet. Gynecol. Reprod. Biol., 95: 92-96.

Pandey, R., R. Kumar, S.P. Singh, D.K. Saxena and S.P. Srivastava, 1999. Male reproductive effect of nickel sulphate in mice. BioMetals, 12: 339-346.

Pandey, R. and S.P. Srivastava, 2000. Spermatotoxic effects of nickel in mice. Bull. Environ. Contam. Toxicol., 64: 161-167.

Pandey, R. and S.P. Singh, 2002. Effects of molybdenum on fertility of male rats. BioMetals, 15: 65-72.

Pant, N., R. Kumar, R.C. Murthy and S.P. Srivastava, 2001. Male reproductive effect of arsenic in mice. BioMetals, 14: 113-117.

Pant, N., R.C. Murthy and S.P. Srivastava, 2004. Male reproductive toxicity of sodium arsenite in mice. Hum. Exp. Toxicol., 23: 399-403.

Perez Romera, E., E. Munoz, F. Mohamed, S. Dominguez and L. Scardapane *et al*., 2000. Lithium effect on testicular tissue and spermatozoa of viscacha (*Lagostomus maximus*). A comparative study with rats. J. Trace Elem. Med. Biol., 14: 81-83.

Ponnapakkam, T.P., K.S. Bailey, K.A. Graves and M.B. Iszard, 2003. Assessment of male reproductive system in the CD-1 mice following oral manganese exposure. Reprod. Toxicol., 7: 547-551.

Ragan, H.A. and T.J. Mast, 1990. Cadmium inhalation and male reproductive toxicity. Rev. Environ. Contam. Toxicol., 114: 1-22.

Rao, M.V. and P.S. Sharma, 2001. Protective effect of vitamin E against mercuric chloride reproductive toxicity in male mice. Reprod. Toxicol., 15: 705-712.

Rignell-Hydbom, A., A. Axmon, T. Lundh, B.A. Jonsson, T. Tiido and M. Spano, 2007. Dietary exposure to methyl mercury and PCB and the associations with semen parameters among Swedish fishermen. Environ. Health, 6: 14-14.

Santos, F.W., T. Oro, G. Zeni, J.B. Rocha, P.C. do Nascimento and C.W. Nogueira, 2004. Cadmium induced testicular damage and its response to administration of succimer and diphenyl diselenide in mice. Toxicol. Lett., 152: 255-263.

Sarkar, M., G.R. Chaudhuri, A. Chattopadhyay and N.M. Biswas, 2003. Effect of sodium arsenite on spermatogenesis, plasma gonadotrophins and testosterone in rats. Asian J. Androl., 5: 27-31.

Seethalakshmi, C., T. Flores, A. Kinkead, A. Carboni, R.K. Malhotra and M. Menon, 1992. Effects of subchronic treatment with cis-platinum on testicular function, fertility, pregnancy outcome and progeny. J. Androl., 13: 65-74.

Siu, E.R., D.D. Mruk, C.S. Porto and C.Y. Cheng, 2009. Cadmium-induced testicular injury. Toxicol. Applied Pharmacol., 238: 240-249.

Slivkova, J., M. Popelkova, P. Massanyi, S. Toporcerova and R. Stawarz *et al*., 2009. Concentration of trace elements in human semen and relation to spermatozoa quality. J. Environ. Sci. Health A Tox. Hazard. Subst. Environ. Eng., 44: 370-375.

Sokol, R.Z. and N. Berman, 1991. The effect of age of exposure on lead-induced testicular toxicity. Toxicology, 69: 269-278.

Subramanian, S., G. Rajendiran, P. Sekhar, C. Gowri, P, Govindarajulu and M.M. Aruldhas, 2006. Reproductive toxicity of chromium in adult bonnet monkeys (*Macaca radiata Geoffrey*). Reversible oxidative stress in the semen. Toxicol. Applied Pharmacol., 215: 237-249.

Telisman, S., B. Colak, A. Pizent, J. Jurasovic and P. Cvitkovic, 2007. Reproductive toxicity of low-level lead exposure in men. Environ. Res., 105: 256-266.

Thakur, S.C., S.S. Thakur, S.K. Chaube and S.P. Singh, 2003. Subchronic supplementation of lithium carbonate induces reproductive system toxicity in male rat. Reprod. Toxicol., 17: 683-690.

Thomas, J.W. and S. Moos, 1951. The effect of orally administered molybdenum on growth, spermatogenesis and testes histology of young dairy bulls. Arch. Biochem., 15: 81-88.

Traina, M.E., P. Ade, G. Siepi, E. Urbani and M.G. Petrelli, 1994. A review of the effect of pesticide formulations on male fertility. Int. J. Environ. Health Res., 4: 38-47.

Turgut, G., G. Abban, S. Turgut and G. Take, 2003. Effect of Overdose Zinc on mouse testis and its relation with sperm count and motility. Biol. Trace Elem. Res., 96: 271-278.

Veado, M.A.R.V., I.A. Arante, A.H. Oliveira, M.R.M.G. Almeida, R.A. Miguel, M.I. Severo and H.L. Cabaleiro, 2006. Metal pollution in the environment of minas gerais state-Brazil. Environ. Monit. Assess., 117: 157-172.

Waalkes, M.P., S. Rehm and D.E. Devor, 1997. The effects of continuous testosterone exposure on spontaneous and cadmium-induced tumors in the male Fischer (F344/NCr) rat: Loss of testicular response. Toxicol. Applied Pharmacol., 142: 40-46.

Waltschewa, W., M. Slatewa and I. Michailow, 1972. Testicular changes due to long-term administration of nickel sulphate in rats. Exp. Pathol. (Jena)., 6: 116-120.

Yang, H.S., D.K. Han, J.R. Kim and J.C. Sim, 2006. Effects of- tocopherol on cadmium-induced toxicity in rat testis and spermatogenesis. J. Korean Med. Sci., 21: 445-451.

Yasmina, M. and C. Abdennour, 2008. Influence of vitamin C on testicular functions of domestic rabbit *Oryctolagus cuniculus* under mercury exposure. Eur. J. Sci. Res., 22: 197-204.

Yousef, M.I., A.M. El-Morsy and M.S. Hassan, 2005. Aluminium-induced deterioration in reproductive performance and seminal plasma biochemistry of male rabbits: Protective role of ascorbic acid. Toxicology, 215: 97-107.

Yousef, M.I., F.M. El-Demerdash, K.I. Kamil and F.A.M. Elaswad, 2006. Ameliorating effect of folic acid on chromium (VI)-induced changes in reproductive performance and seminal plasma biochemistry in male rabbits. Reprod. Toxicol., 21: 322-328.

Zarnescu, O. and G. Zamfirescu, 2006. Effects of lithium carbonate on rat seminiferous tubules: An ultrastructural study. Int. J. Androl., 29: 576-582.