Drug and Chemical Toxicology, 2012; Early Online: 1–16
© 2012 Informa Healthcare USA, Inc.
ISSN 0148-0545 print/ISSN 1525-6014 online
DOI: 10.3109/01480545.2012.710631

informa
healthcare

REVIEW ARTICLE

Environmental and occupational exposure of metals and their role in male reproductive functions

Pallav Sengupta

Department of Physiology, Vidyasagar College for Women, University of Calcutta, Kolkata, West Bengal, India

Abstract
This review summarizes the effects of more than 20 metals that, research has indicated, may influence male reproductive health. Though males lack an apparent, easily measurable reproductive cycle, progress has been made in evaluating tests to identify chemical hazards and estimate reproductive health risks. Some agents discussed in this review are well known to have potential toxic effects on the male reproductive system, whereas some are not so well established in toxicology. This review attempts to cover most of the known toxicants and their effects on male fertility. The literature suggests a need for further research in those chemicals that are reactive and capable of covalent interactions in biological systems, as well as those defined as mutagens and/or carcinogens, to cause aneuploidy or other chromosomal aberrations, affect sperm motility *in vitro*, share hormonal activity or affect hormone action, and those that act directly or indirectly to affect the hypothalamo-pituitary-gonadal axis.

Keywords: metal, arsenic, cadmium, calcium, male infertility, reproduction, magnesium

Copyright © 2012 Informa UK Limited
Not for Sale or Commercial Distribution
Unauthorized use prohibited. Authorised users can download,
display, view and print a single copy for personal use

Introduction

It has been suggested that during the past five decades, human sperm counts have declined and the occurrence of testicular cancer and cryptorchidism has increased. Though males lack an obvious, easily measurable reproductive cycle, and the primary clinical indicator, semen analysis, offers uncertain clues to reproductive performance, progress is being made in developing and evaluating tests to identify chemical hazards and estimate human health risks (Queiroz and Waissmann, 2006). Mammalian male reproductive function can be affected through a direct effect on the testis, resulting in decreased or altered sperm production, through impairment of the accessory sex gland secretions, and indirectly through the neuroendocrine system, causing hormonal imbalance (Chandra et al., 2012a). Adverse effects on male fertility include altered genetic material of sperm, contributing to altered spermatogenesis, pregnancy loss, or genetic disease in offspring. Common endpoints for the evaluation of male reproductive function include size of testis, semen quality, secretory function of the prostate and seminal vesicles, reproductive endocrine function, impotence or reduced libido, and fertility (Nordberg et al., 2005). Current evidence suggests that there may be environmental reasons for deteriorating sperm quality, including occupational exposure to various metals, chemicals, heat, and radiation. In addition, exposure to pesticides has been linked to alterations in spermatogenesis (Sinclair, 2000).

When assessing reproductive effects of a certain metal on male reproductive health, one must make an allowance for possible influences of concomitant exposures to other toxic and essential metals; these may act additively, synergistically, or antagonistically. Certain toxic metals, such as lead and cadmium, are pervasive in the human environment and accumulate in the human body over a lifetime; biomarkers of lead and cadmium exposure commonly correlate with age, smoking habits, and alcohol consumption (Lin et al., 2010).

Recent evidences indicate that the human male reproductive capacity has deteriorated considerably during the past five decades. In industrialized countries, a substantial number of couples seek *in vitro* fertilization

Address for Correspondence: Pallav Sengupta, Department of Physiology, Vidyasagar College for Women, University of Calcutta, 39 Sankar Ghosh Lane, Kolkata 700 006, West Bengal, India; Fax: +91 033 2241 3018; E-mail: sunny_pallav_1984@yahoo.co.in

(Received 15 February 2012; revised 25 June 2012; accepted 25 June 2012)

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

(IVF) or intracytoplasmic sperm injection (ICSI) because of poor semen quality (Nordberg et al., 2005). Data collected over the last 30 years have shown disturbing trends in male reproductive health. An earlier report from Scotland revealed that men born after 1970 had a sperm count 25% lower than those born before 1959—an average decline of 2.1% a year (Brown, 1999). The lower sperm count was also associated with poor semen quality (Waissmann, 2002). Further, large differences in mean sperm concentration between countries, and between different locations within a country, have been observed.

The human male has a relatively low fertility potential, compared with other mammals. For example, the number of sperm per human ejaculate is typically only 2- to 4-fold higher than the number at which fertility is significantly reduced, whereas the number of sperm in rat, rabbit, or bull ejaculate is many times (up to 1,400-fold) the number that will produce maximum fertility (Working, 1988). Human males have markedly smaller relative testis size and the lowest rate of daily sperm production per gram of testis, by a factor of more than 3, compared with the mouse, rat, or monkey. The percentages of progressively motile sperm and morphologically healthy sperm in human semen are also considerably lower than in experimental animals (Working, 1988). The human male may be more susceptible than the rat to metal toxicity, possibly because of poorer efficacy of the antioxidant defense system and greater vulnerability to oxidative damage to sperm DNA and sulfhydryl (–SH) groups required for the maintenance of sperm maturation and motility. Because of differences among species in reproductive endpoints and in the route level, and duration of metal exposure, the experimental animal data may be useful for estimates of allowable human exposure (Sengupta, 2011a; Sengupta, 2012).

Although experimental animal and *in vitro* studies have indicated adverse reproductive effects of high doses of many metals and beneficial or protective effects of some essential metals (particularly zinc, selenium, and magnesium), the internal metal dose was often not measured and relatively few studies have evaluated the effects of long-term moderate oral exposure. For most metals, data relevant to humans are scanty and are usually limited by inadequate controls and adjustments for the influence of potentially confounding variables (Nordberg et al., 2005).

Male reproductive tract target sites

An endocrine disruptor can affect several potential target sites in the male reproductive tract, with the most important being the testes, which usually exist in pairs and are the sites of spermatogenesis and androgen production. There are para- and autocrine regulations in various compartments of the testis that are under endocrine influences from the pituitary and hypothalamus.

Table 1. Male reproductive tract target sites.

Potential sites	Functions	Effects of metals	Evaluative tests
Sertoli cells	Sertoli cells or "nurse cells" establish the blood-testis barrier by virtue of tight junctions. The luminal environment, as controlled by these Sertoli cells, is under the influence of FSH and inhibin. These Sertoli cells: 1) provide nourishment for the developing sperm cells; 2) destroy defective sperm cells; 3) secrete fluid that helps in the transport of sperm into the epididymis; and 4) release the hormone inhibin that helps regulate sperm production.	↓ HPG-axis, ↓ spermatogenesis, CNS effects, testicular damage	Receptor analysis, RIA; *in vitro* production and hormone assay
Leydig cells	Produce testosterone under the control of LH from the pituitary. These cells arise from interstitial mesenchymal tissue between the tubules during week 8 of human embryonic development. They are located in the connective tissue between the seminiferous tubules.		Receptor analysis, RIA; *In vitro* tests (coculture), morphology
Spermatogenesis	Spermatogenesis is a chronological process spanning approximately 72 days in humans and 40–50 days in rodents (depending upon species). During this period, the immature germ cells (undifferentiated spermatogonia) develop into highly specialized spermatozoa in a cyclic manner. Spermatogonia undergo several mitotic divisions to generate a large population of primary spermatocytes, which produce haploid spermatids by two meiotic cell divisions. Spermiogenesis is the transformation of spermatids into elongated flagellar germ cells capable of motility. The release of mature germ cells is known as spermiation.		Germ cell count and % tubules without germ cells, spermatid counts and % tubules with luminal sperm, germ-cell culture, morphology
Epididymis	Sperm maturation		Histopathology, biochemical tests
Seminal fluid	Daily sperm production		Spermatid counts, semen evaluation
Brain	Hypothalamic-pituitary axis		Pituitary cell culture, hypothalamus perfusion histopathology, hormone assay

RIA, radioimmunoassay.

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

Approximately 80% of the testicular mass consists of highly coiled seminiferous tubules within which spermatogenesis takes place. The remaining 20% consists of Leydig cells and Sertoli cells, whose main job is to establish healthy spermatogenesis. Spermatozoa are the haploid germ cells responsible for fertilization and species propagation (Roy Chowdhury, 2009) (Table 1).

Role of metals in male reproductive health

Potential toxic effects of more than 20 metals (i.e., lead, cadmium, chromium, arsenic, calcium, and so on), those that cause alteration in sperm morphology, count, motility, as well as biochemical and endocrine disruptions, as well as those metals that are beneficial or protective for male reproductive functions (particularly zinc, selenium, and magnesium) are discussed in this review.

Arsenic

Arsenicals are widespread in the environment as a result of natural and anthropogenic occurrence. Ingestion of contaminated drinking water is the major route for human exposure to arsenic (Neiger and Osweiler, 1985). Arsenic exposure causes both acute and chronic toxicity in humans. Exposure of mice and rats to high doses of inorganic arsenic can adversely affect spermatogenesis and can decrease testicular and accessory sex organ weights and serum levels of lutenizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (Pant et al., 2001; Sarkar et al., 2003). Chronic oral exposure of mice to sodium arsenite in drinking water is reported to cause significant accumulation of arsenic in the testis, epididymis, seminal vesicles, and prostate, a decrease in the absolute and relative testicular weight, but not of epididymal and accessory sex organ weights, a decrease in sperm count and motility, increase in abnormal sperm morphology, and changes in the activities of testicular enzymes (Pant et al., 2004). Exposure of sodium arsenite in drinking water is also shown to produce steroidogenic dysfunction that leads to impairment of spermatogenesis in rats (Sarkar et al., 2003). Few recent investigations have shown that arsenic in drinking water is associated with oxidative stress (OS) (Chang et al., 2007) of genotoxicity in testicular tissue of mice (Biswas et al., 2006). On the other hand, recent studies suggest that arsenic causes testicular toxicity, probably by affecting the pituitary-testicular axis (Jana et al., 2006). But, the dose- and duration-dependent effect of sodium arsenite in drinking water on testicular tissue of mice is not well established.

Bismuth

The most common exposures to bismuth include working in close correlation with the element; for instance, a plumber who uses a lot of solder can be exposed to bismuth by breathing in the fumes from soldering in a confined space. Bismuth compounds (e.g., bismuth subsalicylate, bismuth oxychloride, and bismuth subgallate) are used in a number of applications where it can come in direct contact with the body (Stoltenberg et al., 2002). The consumption of bismuth is increasing, and knowledge of the potential teratogenic and reproductive damage of bismuth exposure is fragmentary. Bismuth treatment has been reported to show its accumulation in Leydig cells, with a subsequent reduction in serum testosterone levels. In addition, the mean number of Leydig cells in the bismuth-treated groups is reported to be less than the control (Pedersen et al., 2003). Bismuth exposure has been stated to reduce sperm creatine kinase activity, feasibly by displacing the Mg^{+2} from this enzyme (Ghaffari and Motlagh, 2011). In some studies, trace of bismuth in the testis and pituitary glands of Wistar rats were found after they were injected intraperitoneally (i.p.). Large amounts of bismuth were found to be concentrated in the lysosomes of Leydig cells. Reports suggested that neither FSH nor LH were affected, compared to their corresponding controls. The selective uptake of bismuth in Leydig cells, followed by decreased testosterone levels, has been emphasized as a potential hazard of bismuth-provoked male reproductive impairment in those reports (Stoltenberg et al., 2002).

Boron

Boron is not present in nature in its elemental form. It is found combined in borax, boric acid, kernite, ulexite, colemanite, and borates. Volcanic spring waters sometimes contain boric acids. Borates are mined in the United States, Tibet, Chile, and Turkey, with world production being approximately 2 million tons per year. Miners are generally exposed to this element (Robbins et al., 2007). Earlier studies in human workers and populations have not identified adverse effects of boron exposure on fertility, but outcome measures in these studies were relatively insensitive, based mainly on family size, and did not include an evaluation of semen endpoints. A recent study of men working in boron mining or processing in the Liaoning province in northeast China has been published in several Chinese and a few English-language articles. Employed men living in the same community and in a remote community were used as controls. Boron workers had a mean daily boron intake of 31.3 mg/day, and a subset of these men, employed at a plant where there was heavy boron contamination of the water supply, had an estimated mean daily boron intake of 125 mg/day. Estimates of mean daily boron intake in local community and remote background controls were 4.25 and 1.40 mg/day, respectively. Reproductive outcomes in the wives of 945 boron workers were not significantly different from outcomes in the wives of 249 background control men after adjustment for potential confounders. There were no statistically significant differences in semen characteristics between exposure groups, including in the highly exposed subset, except that sperm Y/X ratio was reduced in boron workers. Within exposure groups, the Y/X ratio did not correlate with boron concentration in blood, semen, and urine. In conclusion, whereas boron has been shown to adversely affect male reproduction

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

in laboratory animals, there is no clear evidence of male reproductive effects attributable to boron in studies of highly exposed workers (Scialli et al., 2010). Boron treatment of rats, mice, and dogs has been associated with testicular toxicity, characterized by inhibited spermiation at lower dose levels and a reduction in epididymal sperm count at higher dose levels (Robbins et al., 2007). Results of some studies on laboratory animals (i.e., mice) showed significant increase in weight, volume, and size of testicles and seminal vesicles of treated animals; histological analysis of testicles showed an epithelium notoriously altered with few spermatids. Spermatogonia were present with picnotic nuclei, suggesting apoptosis. In conclusion, boron in high doses produces important cytotoxic effects, with degeneration of the epithelium of seminiferous tubules, possibly inhibiting spermiation, causing testicular hypertrophy, altering masculine reproductive patterns, and a reduction in fertility of mice (Espinoza-Navarro et al., 2007).

Cadmium

The main exposure to cadmium, in people, occurs through the consumption of foods and drinking water, the inhalation of cadmium particles from ambient air or cigarette smoke, and the incidental ingestion of contaminated dust or soil. Foods (e.g., grains, cereals, and leafy vegetables) that have been contaminated through water and crops grown on polluted soil are the highest source of cadmium exposure for the general population. People with low calcium, protein, or iron reserves appear to absorb cadmium more efficiently and may be at increased risk of developing toxicity (Benoff et al., 1997). Cadmium is also present as an endocrine disrupting compound (EDC) that interferes with the synthesis and regulation of several hormones in both females and males (Cheng et al., 2011).

Even though various cadmium-induced effects on the male reproductive system have been described, there is little conclusive published evidence of cadmium-related effects on semen quality, sex hormones, or fertility in human males. Most studies have failed to adjust for the influence of potentially confounding variables, such as age, smoking habits, alcohol consumption, and the body status of the relevant metals, particularly lead, zinc, and selenium. In men not occupationally exposed to cadmium, a significant increase in cadmium levels in blood and seminal plasma has been related to smoking habits (Telišman et al., 2000). However, in addition to increasing individual exposure to cadmium, smoking itself may adversely affect male reproductive function by mechanisms of OS involving other compounds present in cigarette smoke (Lin et al., 2010). Published data on men with suspect infertility (including nonsmokers and smokers) showed a significant positive correlation between abnormal sperm morphology and blood cadmium levels, but not with seminal plasma cadmium levels (Telišman et al., 2000). An inverse correlation has been reported on between testis size and blood cadmium (Jurasovíc et al., 2004), sperm motility and blood cadmium (Telišman et al., 2000), semen volume and either blood cadmium (Chia et al., 1992) or seminal plasma cadmium (Chia et al., 1994), and sperm concentration and sperm count with respect to blood cadmium levels (Chia et al., 1994). Several other studies reported no significant correlations between semen quality and cadmium levels in semen, seminal plasma, or blood. Nonsmoking patients with varicocele had significantly higher cadmium and lower zinc levels in the seminal plasma, compared to fertile subjects (Benoff et al., 1997). In nonsmokers and nonconsumers of alcohol, a significant positive correlation was found between sperm DNA oxidative damage and seminal plasma levels of both cadmium and lead, whereas an inverse correlation was found with seminal plasma selenium levels, suggesting that cadmium may contribute to sperm DNA oxidative damage and thereby affect semen quality (Xu et al., 2003); however, the study did not evaluate the combined effect or interaction of cadmium, lead, and selenium concerning these endpoints. A study on Chinese men environmentally exposed to cadmium showed a significant dose-response trend of increasing urinary cadmium and the prevalence of cases with abnormal levels of prostate-specific antigen in serum. Further, subjects with abnormal findings on digitorectal examination of the prostate had significantly higher blood cadmium, suggesting that increased chronic cadmium exposure can cause injury to the human prostate (Zeng et al., 2004). In some other studies, significant relationships were found between increasing serum levels of estradiol, FSH, and testosterone that have been found with respect to blood cadmium (Jurasovíc et al., 2004). Another study of men not occupationally exposed to cadmium also showed a significant relationship between increasing serum testosterone and blood cadmium levels (Telišman et al., 2000).

Many studies in experimental animals have shown that the mammalian testis is highly vulnerable to cadmium, which can cause germinal cell damage and testicular necrosis, possibly through a direct effect on the testicular vasculature, which may exert a secondary action by lowering testosterone production and thereby also affecting accessory genital organs, including the prostate (Lymberopoulos et al., 2003). The following acute effects have been reported in experimental animals injected with soluble cadmium salts: decreased serum testosterone; a decreased size and weight of the testes, epididymis, vas deferens, prostate and seminal vesicles; decreased sperm production and motility; and suppressed libido and reproductive capacity (Waalkes and Rehm, 1994). Testicular atrophy and necrosis and decreased fertility have been observed in animals at nearly fatal doses of cadmium (Bomhard et al., 1987). In rats, long-term exposure to cadmium through the drinking water (10 mg/L for 52 weeks) led to pathological testicular changes, as well as liver and kidney damage, whereas reproductive capacity was reduced in 40% of animals (Saygi et al., 1991). A synergistic effect of lead and cadmium on testicular

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

injury in rats has been reported on (Saxena et al., 1989). In contrast, a protective effect against male reproductive toxicity of cadmium was observed in animals treated with zinc (Saxena et al., 1989), selenium (Jones et al., 1997), or –SH-containing compounds, such as cysteine, glutathione, and metallothionein (MT) (Nordberg et al., 1971). Neither small chronic doses of cadmium, which induce MT biosynthesis nor injections of cadmium partially bound to MT cause testicular necrosis (Nordberg et al., 1971).

Calcium

Excess calcium exposure in the body may be caused by too much intake of the increasing number of calcium-fortified food products or may be the result of calcium oversupplementation or drinking of hard water containing excessive calcium salt (Chandra et al., 2012a). Calcium is indispensable for healthy functioning of male reproduction. But, many reports on its detrimental effect on male reproduction have also been described. Some studies showed it could also be used as chemocastrative agent (Sengupta and Chandra, 2009; Canpolat et al., 2006). Most of the studies are carried out in laboratory animals by injecting calcium chloride intratesticularly (Canpolat et al., 2006; Jana and Samanta, 2006). But, some studies also showed that supplementation of excess calcium in the diet for a long duration may also disrupt male reproductive function (Chandra et al., 2012b). Calcium was shown to generate free radicals, thus causing oxidation of lipids of testicular germ cells and Leydig cells; generation of free radicals causes activation of the testicular antioxidant defense mechanism (Chandra et al., 2012b; Jana and Samanta, 2006). Testicular free radicals also affect healthy spermatogenesis processes. Reproductive parameters showed a significant decrease, such as in testicular and accessory sex organ weight, epididymal sperm count, testicular steroidogenic enzyme [Δ^5 3β-hydroxy steroid dehydrogenase (HSD) & 17β-hydroxy steroid dehydrogenase] activities, serum testosterone, LH, and FSH. Testicular histoarchitecture also showed degenerative changes (Sengupta et al., 2011b). Generated free radicals are also reported to act by hypothalamo-pituitary-adrenal (HPA) axis. Thus, interaction between the hypothalamo-pituitary-gonadal (HPG) and HPA axes results in the structural and functional disruption of male reproduction (Sengupta et al., 2011c).

Chromium

Chromium exposure may occur by breathing air, drinking water, or eating food containing chromium or through skin contact with chromium or chromium compounds. The level of chromium in air and water is generally low. The concentration of total chromium in air (both CrIII and CrVI) generally ranges between 0.01 and 0.03 μg/m^3 (Hui, 2002). Chromium concentrations in drinking water (mostly as CrIII) are generally very low (less than 2 ppb). Contaminated well water may contain CrVI. Chromium may also occur by household utensils, wood preservatives, cement, cleaning products, textiles, and tanned leather (Lotrich, et al., 2006). People who work in industries that process or use chromium or chromium compounds can be exposed to higher than normal levels of chromium. An estimated 305,000 workers in the United States are potentially exposed to chromium and chromium-containing compounds in the workplace. Hexavalent chromium (CrVI), used in more than 50 industries, is an important metal pollutant (Barceloux, 1999). Several systemic toxicities of CrVI have been demonstrated in experimental animals *in vivo* and *in vitro* (Bagchi et al., 2002; Levina et al., 2003). However, reproductive toxicity of chromium has been underplayed since the report of Bonde (1993), which stated that low-level exposure to CrVI might not be a major hazard affecting spermatogenesis in stainless-steel welders. Even in a recent review, Bonde (2002) emphasized the need for additional data to recognize the reproductive toxicity of chromium. Nevertheless, a number of investigations using laboratory animals have pointed out the testicular toxicity of CrVI (Chowdhury and Mitra, 1995; Sutherland et al., 2000). Two recent reports also correlated chronic occupational exposure to CrVI to abnormal semen quality in men (Li et al., 2001; Danadevi et al., 2003), though the amount and type of CrVI used by Li et al. were questioned (Duffus, 2002). Li et al. showed male workers exposed to chromium (VI) for 1–15 years in an electroplating factory, compared to unexposed workers (Li et al., 2001), had significantly decreased sperm concentration (by 47%), sperm motility, and seminal plasma levels of zinc, lactate dehydrogenase (LDH), and the LDH isoenzyme, LDH-C4, whereas serum FSH was significantly increased; serum chromium levels in exposed workers were 1.40±0.01 μmol/L. Another study of male welders, whose blood chromium levels were 131.0±52.6 μg/L, showed significantly decreased sperm concentration (by 67%) in exposed workers, compared to controls, and an inverse correlation between sperm concentration and blood chromium levels in exposed workers (Dandevi et al., 2003).

Animal exposure to high doses of chromium (III or VI) has been shown to adversely affect spermatogenesis. Chromium (VI) is considerably more toxic (Ernst, 1990; Ernst and Bonde, 1992; Li et al., 2001) and may involve OS. This is evidenced by increased lipid peroxidation (LPO) in the testes, decreased sperm count, and increased abnormal sperm morphology of mice exposed to chromium (VI), each of which was partially preventable by tsupplementation with antioxidants, such as vitamin E and, especially, vitamin C (Acharya et al., 2004). In addition, uptake of CrVI by the testis and its subsequent reduction to trivalent chromium (CrIII) are well known (Sipowicz et al., 1997; Sutherland et al., 2000). Recent reports showed that the accumulation of uni- and multinucleate germ cells in the epididymal lumen of monkeys treated with CrVI caused ductal obstruction (Aruldhas et al., 2004).

Cobalt

Cobalt is an essential oligoelement that enters in the composition of vitamin B_{12} (Lauwerys and Lison, 1994).

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

For the general population, food and beverages represent the main source of cobalt exposure. Traces of cobalt are also present in cement and various household products. In industry, the potential for exposure to cobalt is particularly important during the production of cobalt powder, the production, processing and use of hard metals, the polishing of diamonds with cobalt containing disks, and the processing of cobalt alloys. Except in the production of cobalt powders, these activities involve exposure not only to cobalt, but also to other substances, such as tungsten carbide, iron, and diamond, which may modulate the biological reactivity of cobalt. Cobalt salts are used for the preparation of enamels and pigments. Chronic exposure of male mice to cobalt chloride dramatically affected their reproductive potential, whereas acute administration had minimal effects (Pedigo et al., 1988). Acute exposure, followed by evaluation weekly over a 7-week period, revealed no significant changes in epididymal sperm concentration or testicular weight. However, small, but significant, decreases in fertility at weeks 2 and 3 of the study were observed. Sperm motility was depressed only during week 1 of the study (Kumar et al., 1990). In chronic studies, cobalt affected fertility in a time- and dose-dependent manner. There was a decrease in testicular weight, epididymal sperm concentration, and fertility. Sperm motility was also depressed. Serum testosterone levels were dramatically increased in cobalt-treated animals, whereas FSH and LH serum levels were normal. It appears that cobalt is directly or indirectly interfering with spermatogenesis and with local regulatory mechanisms in testosterone synthesis (Pedigo et al., 1988). Cobalt is an essential oligoelement for mammals, not a cumulative toxin, but chronic exposure induces negative effects on the organism. Data from the literature evidenced that in experimental animals, cobalt impaired male reproductive organs and fertility when applied chronically. Some other studies showed the effect of cobalt on pubertal male progeny of female mice treated with cobalt in late pregnancy and during the suckling period. Significant reduction in macroscopic parameters, such as as body weight and 20% decrease (nonsignificant) of testicular and epididymal weight as well as in testis/body-weight index, was found. The effect of cobalt on male progeny could be explained with the transplacental route of exposure and with the possible transfer of cobalt into mothers' milk. The negative effect of cobalt was not observed in midpuberty (day 25), with the exception of epididymal weight, which was not compensated, suggesting that epididymis is more sensitive to cobalt treatment. Those studies concluded that exposure to cobalt during the peri- and postnatal period affected body weight during puberty, but did not significantly reduce reproductive organ growth (Madzharova et al., 2010). However, as in other studies, it could be concluded that a negative effect of cobalt on later life could not be rule out and that cobalt might be considered as a possible risk factor for male reproductive health (Pedigo et al., 1988; Becker and Smith, 1951).

Copper

Copper can be found in many kinds of food, in drinking water, and in air. The absorption of copper is necessary, because copper is a trace element that is essential for human health. Although humans can handle proportionally large concentrations of copper, too much copper can still cause eminent health problems. But, people that live near smelters that process copper ore into metal do experience this kind of exposure. People that live in houses that still have copper plumbing are exposed to higher levels of copper than most people, because copper is released into their drinking water through the corrosion of pipes. Occupational exposure to copper often occurs. In the working environment, copper contagion can lead to a flu-like condition known as metal fever (Armstrong et al., 1983). In the reproductive system, the effect of copper on spermatozoa was studied as early as 1956 and has given rise to numerous studies, and the assay findings have recurred in all the tissues of the male reproductive system, with considerable individual differences, the cause of which is not understood. Its role in the sperm is unclear, but it appears to be involved in spermatozoa mobility and it may also act on pituitary receptors, which control the release of LH. Copper can act on FSH receptors, interfering in spermatogenesis. In the seminal fluid, the level of copper appears to fall in cases of azoospermia and to increase in oligo- and asthenozoospermia, but the findings of different investigators are somewhat contradictory, and some investigators do not report on any correlation between the seminal level of copper and the number or mobility of the gametes (Skandhan, 1992). It is true that the concentrations in the ejaculate vary considerably from one day to the next and that they also vary in different fractions from a single ejaculate. Copper reduces oxidative processes and glucose consumption, which reduces or abolishes mobility: this property is exploited in intrauterine devices (IUDs). The use of copper for male contraception has given rise to experimental implantations at various sites within the male system—lumen of the deferens, epididymis, seminal vesicle, and scrotum—and the mobility of spermatozoa was abolished in all cases (Eidi et al., 2010; Chattopadhyay et al., 2005). Tissue toxicity makes it impossible to use this method in human practice. This is why research is concentrating on preparations able to release tiny quantities of the metal in a regular continuous fashion until testicular function is blocked without damaging the tissues (Skandhan, 1992).

Fluoride

Fluoride is found in drinking water, toothpaste, soda and juices, fluoridated salts, et al. But, for fluoride toxicity, fluoridated water is one of the biggest culprits; total exposure to fluoride is one of the factors that ultimately determine one's level of risk for the adverse effects of fluoride. Therefore, it is important to reduce the level of exposure to fluoride from all sources. In some reports, it has been described that when sexually mature male Swiss mice were exposed to 100, 200, and 300 ppm of sodium fluoride

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

(NaF) in their drinking water for 4 weeks or 10 weeks, fertility was significantly reduced at all three concentrations by exposure for 10 weeks, but not for 4 weeks. The number of implantation sites and viable fetuses was significantly reduced in females mated with males that had ingested NaF at a concentration of 200 ppm for 10 weeks. Relative weights of seminal vesicles and preputial glands were significantly increased in mice exposed to 200 and 300 ppm of NaF for 4 weeks, but not in mice exposed for 10 weeks. These results indicate that long-term ingestion of NaF adversely affects fertility in male mice (Darmani et al., 2001; Elbetieha et al., 2000). The most important consequences of these fluoride exposures are changes in the structure and functional behavior of spermatozoa, disruption of spermatogenesis, and disturbances of multiple hormone systems that affect male reproduction. Changes in spermatozoa result from oxidative damage, zinc deficiency, and disturbed signal transduction. There is evidence that fluoride interferes with spermatogenesis by depressing levels of epidermal growth factor (EGF) and epidermal growth factor receptor (EGFR), modifying G-protein signaling, diminishing levels of testosterone and its androgen receptor (AR), and disturbing levels of estradiol. Further, fluoride is also known to interfere with thyroid hormone metabolism, which directly and indirectly affects not only spermatogenesis, but also other reproductive functions (Long et al., 2009). Although fluoride appears to exert its toxic effects in the male reproductive system through these pathways, the molecular details are still poorly understood. The growing evidence that fluoride overexposure leads to male reproductive toxicity through multiple pathways indicates that an assessment of chronic fluoride exposures in human and animal populations is urgently required.

Gold

For centuries, Ayurveda, the ancient medicine of India, mentions the role of gold in the treatment of male infertility (Tripathi, 1998; Sharma et al., 1979). "*Swarna bhasma*" (ash of gold) has been used with good results by Ayurvedic practitioners in the treatment of infertility (Godatvar, 1995; Shrinivas, 1998; Thaker, 2000). The presence of gold in the body is thought to be a contaminant from environmental elements, such as sea water, and total human body content of gold is calculated to be 0.1 mg. Oser (1975) and Bondani *et al*. (1973) considered semen to be a source of excretion for electrolytes, although this may not be true for gold. Gold has been claimed to have a beneficial effect on testicular function and sperm. Jain et al. (2010) has shown that estimated gold was after complete digestion (oxidation of organic matters; hence, whatever amount of gold is detected denotes the levels in seminal plasma as well as the sperm itself) in whole semen (seminal plasma and sperm) is quite high, when compared with the results of Skandhan (1981). Though Skandhan, in his study, had not included the sperm and did not mention the digestion procedure (i.e., to convert all organically bound gold into inorganic forms, which is the detectable form), which could be the possible cause for the high values of gold in results of Jain et al. However, the literature available correlating the effect of gold on male reproductive health is quite scanty, and further studies are required to make scientific correlation of gold and male infertility.

Indium

Workers in welding and semiconductor industries were found to be exposed to relatively high levels of indium. Indium is increasingly used in a variety of industries, and though there are few studies of its developmental toxicity, there are no reports of its potential reproductive toxicity, though a few studies carried out in experimental animals showed some detrimental changes to the male reproductive tract (i.e., vacuolization in the epithelium in indium-treated hamsters, which is a histopathologic change) may be responsible for the testicular damage. The severity and nature of the adverse effect is variable and can be influenced by factors such as sex, level of exposure, and individual sensitivity to the chemical. Its effects on the male reproductive system can include such things as altered sexual behavior, altered fertility, and problems with sperm shape or count (Chaplin et al., 1995). The weights of the testis and epididymis were not decreased, and the caudal sperm count was found to be decreased in treated animals (Omura et al., 2002). In addition, indium exposure was also reported to reduce sperm creatine kinase activity (Ghaffari and Motlagh, 2011). Change in the testicular damage caused by indium arsenide (InAs) and indium phosphide (InP) was examined during 2 years after repetitive intratracheal instillations in hamsters. Both InAs and InP were proven to be definite testicular toxicants. Both materials were reported to decrease reproductive organ weight and caudal sperm count and caused severe histopathologic changes in the testes. InAs-induced testicular damage was more potent than InP-induced testicular damage. In histopathologic examination, vacuolization of seminiferous epithelium was frequently observed as an early histopathologic change, and spermatogonia remained, in general, even in the seminiferous tubules with severe histopathologic changes in both groups. lt is therefore estimated that Sertoli cells, not stem cell spermatogonia, were the target cells of these indium-containing compound semiconductor materials (Omura et al., 2000).

Lead

Humans are exposed occupationally and environmentally to metal aerosols, including lead. It accumulates in male reproductive organs that result in male infertility. Over the last two centuries, many studies have shown the effect of lead on male reproductive physiology. Several studies of men occupationally exposed to lead have shown significantly reduced semen quality, but not affected reproductive endocrine function (Telišman et al., 2000), whereas studies that measured only hormonal profiles (e.g., serum FSH, LH, testosterone, and sex-hormone–binding

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

globulin level) have shown no relevant effect on male reproductive endocrine profile (Erfurth et al., 2001).

A decrease in semen volume (Lerda, 1992), sperm concentration, and sperm count (Alexander et al., 1996), sperm motility (Viskum et al., 1999), and an increase in abnormal sperm morphology, particularly at the head of the sperm (Lerda, 1992), and impairment of prostate secretory function, as indicated by decreased seminal plasma zinc level (Wildt et al., 1983), was observed by various studies. Some data suggest that the reproductive effects of lead in men are reversible; a trend toward normalization was found in subjects treated with a lead-chelating agent (Fisher-Fischbein et al., 1987) or after cessation of occupational lead exposure (Viskum et al., 1999). After adjusting for age, smoking, alcohol, blood cadmium, serum zinc, and serum copper, an increase in blood lead was significantly associated with decreasing sperm concentration, counts of total sperm and progressively motile sperm, seminal plasma levels of zinc, acid phosphatase and citric acid, and increasing percentage of pathological sperm with abnormal sperm head morphology.

Abnormal sperm chromatin structure was not significantly related to blood lead levels. However, it seems possible that differences in some lifestyle factors and the body burden of other relevant metals, not controlled for in this study, might have contributed to variations in reproductive parameters among the study population, thereby weakening or masking the relationship between blood lead and reproductive effects (Hamadouche et al., 2009).

Recent data indicate that lead can adversely affect human semen quality, even at blood lead levels <150 μg/L (Jurasovíc et al., 2004). In a study of 123 men who had never been occupationally exposed to metals, the median (range) blood lead values were 57 μg/L (range, 25–149). After adjusting for confounding variables (e.g., age, smoking, alcohol, blood cadmium, and serum copper, zinc, and selenium), an increase in blood lead was significantly associated with decreasing percentages of morphologically healthy and subnormal sperm and with increasing percentages of slow sperm and overly wide sperm. A decrease in δ-aminolevulinic acid dehydrogenase (ALAD) activity was significantly associated with decreasing size of testes and seminal plasma levels of the LDH isoenzyme, LDH-C4 (Jurasovíc et al., 2004). In another study (Benoff et al., 2003), the seminal plasma lead levels of subjects not occupationally exposed to lead were found to inversely correlate with fertilizing capacity of sperm acrosome reaction and the fertilization rate when using the IVF technique, but also with seminal plasma zinc levels. Taken together, these studies suggest that lead may significantly reduce human semen quality, even at low-level lead exposure, that is common for general populations worldwide. Several studies of lead workers have indicated that paternal blood lead levels of approximately 300–400 μg/L are a most likely threshold for the increased rate of spontaneous abortions (Lindbohm et al., 1991), reduced rate of live births (Lin et al., 1996), and prolonged time to pregnancy (Shiau et al., 2004), although inconsistent findings (Joffe et al., 2003) or a minor incompatibility were also reported. An Italian study (Apostoli et al., 2000) reported that, although shorter time to pregnancy (TTP) was found in lead workers, compared to control subjects, within the group of lead workers, a longer TTP was associated with higher blood lead levels and significantly longer TTP was observed at blood lead levels equal to 400 μg/L. A recent study from Taiwan (Shiau et al., 2004) showed a clear dose-response trend of prolonged TTP with respect to increasing paternal blood lead levels; the fecundability ratios (inversely related to TTP) were 0.90, 0.72, 0.52, and 0.40 for blood lead categories <200, 200–290, 300–390, and equal to 400 μg/L, respectively, compared to unexposed men, indicating that even blood lead levels <300 μg/L may prolong TTP. A significantly increased rate of congenital malformations was found in children of occupationally lead-exposed fathers at paternal blood lead levels of 200 μg/L (Sallmén et al., 1992). A reduced sex ratio (reduced male proportion) among offspring of lead-exposed fathers has been observed in some studies (Dickinson and Parker, 1994), but not in others (Min et al., 1996). Several experimental studies in rats, mice, rabbits, or monkeys have indicated that chronic lead exposure for at least 30 days, resulting in current blood lead levels equal to 400 μg/L, was associated with decreased intratesticular or epididymal sperm counts, sperm production rate, sperm motility, and serum testosterone levels, although mainly without significant effect on male fertility, whereas several other studies have shown no significant reproductive effect at comparable blood lead levels (Apostoli et al., 1998). An experimental study in rabbits (Moorman et al., 1998) showed an estimated threshold for reduced sperm count at a blood lead level of 240 μg/L and even lower for several other semen characteristics. A study on the effect of combined exposure to lead and cadmium on the testes of rats (Saxena et al., 1989) showed that animals orally exposed to the combination exhibited significantly more pronounced pathological testicular changes, with a reduction in sperm counts, compared with animals exposed to either of the metals alone. A protective effect of zinc against lead- and cadmium-induced testicular injury in rats was reported on (Batra et al., 1998). With regard to possible mechanisms for a male-related transgenerational effect of lead, an *in vitro* study (Quintanilla-Vega et al., 2000) has shown that lead can compete with or replace zinc in human protamine P2 (HP2), a zinc-containing protein that protects sperm DNA by binding to it during spermatogenesis. Exposure of HP2 to lead resulted in a dose-dependent decrease in the extent of HP2-DNA binding, although lead effects on sperm DNA also contributed to this effect. This may affect sperm chromatin integrity, thereby reducing sperm-fertilizing capacity and causing sperm DNA damage.

Magnesium

Magnesium, an essential element for health and disease has been identified as a cofactor in various enzymatic reactions, including energy metabolism and protein and

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

nucleic acid biosynthesis. Its exposure is only occurring if people consume magnesium-rich foods or consume hard water for a long time (Yang, 1998). Available literature on the effect of excess magnesium on the male reproductive system is insufficient. A few reports suggested the effect of excess dietary magnesium on the male reproductive system (Sengupta et al., 2011d). Treatment of magnesium in adult male rats was at different doses, and durations showed increase in relative weight of testis, but no such change in accessory sex organs, epididymal sperm count, serum testosterone, and LH and FSH levels. Testicular steroidogenic enzymes activities (Δ^5 3β-HSD and 17β-HSD) were found to be elevated after chronic treatment with magnesium. Testicular histoarchitecture also showed no change in tubular structure. Magnesium, on the other hand, was not found to promote oxidative stress, as evidenced by activities of a testicular antioxidant enzyme profile [i.e., superoxide dismutase (SOD) and catalase (CAT)] (Chandra et al., 2012c; Sengupta et al., 2011d).

Manganese

Manganese is found naturally in the environment and is also released into the air from mining and manufacturing operations and from combustion of gasoline additives. In men occupationally exposed to manganese dust, clinical signs of manganism were commonly accompanied with impotence or reduced libido (Emara et al., 1971; Mena et al., 1967; Rodier, 1955), indicating that manganese-related effects were, in part, neurological in origin; they found that men with high manganese levels had a greater than 5-fold higher likelihood of low sperm motility. Low blood manganese levels were also associated with low sperm motility (Wirth et al., 2007). A study of male workers moderately exposed to manganese dust (Lauwerys et al., 1985) showed a significantly reduced rate of live births, compared to a control group. A high single dose of manganese (160 mg of MnO_2/kg by intratracheal instillation) caused degenerative testicular changes and sterility in rabbits (Chandra et al., 1973; Seth et al., 1973). Chronic dietary exposure of young rats to manganese Mn_3O_4 for 224 days resulted in no effect on male fertility at manganese doses <1,100 ppm, whereas at a dose of 3,500 ppm, decreased testicular weight, sperm count, and serum levels of FSH and testosterone were noted, together with general toxic effects (Laskey et al., 1982). In mice orally exposed to manganese acetate for 43 days, a significant decrease in sperm count and motility was observed at doses of 15.0 and 30.0 mg/kg/day, whereas there was no effect on fertility and testicular pathology (Ponnapakkam et al., 2003).

On the other hand, the antioxidative action of Mn^{2+} on various peroxidizing systems (i.e., sperms and neurons) has been studied. It has been found that Mn^{2+} inhibits LPO produced by a free-radical–producing system, but not LPO induced by a single oxygen (Cavallini et al., 1984). Some reports suggested manganese deficiency may cause symptoms such as impaired or depressed reproductive functions (Barber et al., 2005; Singh et al., 1989). It is an essential component of several enzymes, some of which (e.g., SOD, pseudo-CAT, and the photosynthetic oxygen evolving center) are involved in redox processes (Campanella et al., 2005). Manganese has also been designated as a chain-breaking antioxidant because it is able to quench peroxyl radicals (Coassin et al., 1992).

Mercury

Male reproductive toxicity of organic and inorganic mercury has been observed in animals, mainly at dose levels that are otherwise toxic; evidence of a causal relationship in humans is limited because of a small number of studies performed and insufficient control for potentially confounding variables. In workers exposed to mercury vapor, sex-hormone–binding globulin level in serum inversely correlated with duration of exposure, whereas no correlation was observed with serum levels of FSH, LH, and testosterone, neither with respect to duration of exposure nor mercury levels in blood and urine (McGregor and Mason, 1991). A significant positive correlation between serum total testosterone, but not free testosterone, and cumulative mercury exposure was found in workers exposed to mercury vapor for an average of 10 years (Barregärd et al., 1994). No effect on fertility, as assessed by the rate of live births, was observed in male workers chronically exposed to mercury vapor (Lauwerys et al., 1985). An increased rate of spontaneous abortions among wives of workers exposed to mercury vapor was, however, noted at paternal urinary mercury levels >4,000 μg/L; the effect was not significant after controlling for previous miscarriage history (Alcser et al., 1989). In another study of workers exposed to mercury vapor (Cordier et al., 1991), a trend of increasing rate of spontaneous abortions was associated with paternal urinary mercury levels of 1–19 and 20–49 μg/L; however, the study did not address confounding factors, such as smoking and alcohol consumption. In studies of men with suspect infertility, compared to fertile men, nonsignificant association was found between parameters of semen quality and mercury levels in blood (Leung et al., 2001), urine, or ejaculate (Hanf et al., 1996). In another study, an increased risk of subfertility was found to be associated, in a dose-dependent manner, with increasing levels of mercury in hair (Dickman et al., 1999). Both methylmercury and inorganic mercury can accumulate in animal testes, although the uptake and clearance of methylmercury was faster. Exposure of mice to methylmercury or inorganic mercury resulted in adverse effects on spermatogenesis, testicular morphology, and fertility, whereas DNA synthesis in spermatogonia was depressed by methylmercury and, to a lesser extent, by inorganic mercury (Lee and Dixon, 1975). In monkeys dosed with methylmercury (orally 25 μg/kg/day for 20 weeks), decreased sperm motility and increased abnormal sperm tail morphology were observed at subneurotoxic levels; there was no change in testicular morphology and serum testosterone (Mohamed et al., 1987). In rats exposed to

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

methylmercury (0.8, 8.0, or 80 μg/kg twice-weekly in the diet for 19 weeks), significantly decreased intratesticular testosterone and somewhat lowered epididymal sperm count were found in the high-dose group, whereas inverse correlation was observed between fertility and testicular mercury content (Friedmann et al., 1998).

In rats, mice, guinea pigs, and hamsters exposed to inorganic mercury (mercuric chloride i.p. 1, 2, or 5 mg/kg/day for 1 month), the highest dosage caused testicular degeneration and cellular deformation of the seminiferous tubules and the Leydig cells in all species, whereas the lowest dosage caused testicular degeneration only in the hamster; partial degeneration was observed in the rat and mouse, and no change was noted in the guinea pig (Chowdhury and Arora, 1982). In rats orally exposed to mercuric chloride (9 mg/kg/day for 60–180 days), testicular morphological changes and decreased testosterone levels were found (Agrawal and Chansouria, 1989). In mice exposed to inorganic mercury through drinking water (4 ppm of mercuric chloride for 12 weeks), degenerative testicular changes, decreased absolute and relative testicular weight, and decreased epididymal sperm count were found; a protective effect of zinc was reported (Orisakwe et al., 2001). Vitamin E, administered with mercuric chloride (1.25 mg/kg/day) by gavage for 45 days in mice, was protective against reduced epididymal sperm count and sperm motility and viability and resulted in lower concentrations of mercury in the testis, epididymis, and vas deferens (Rao and Sharma, 2001).

Molybdenum

Molybdenum exposure occurs from ingestion of naturally occurring or industrially related contamination of food and water and molybdenum-containing multivitamin/multimineral supplements or from occupational exposure of building materials or consumer products (Seldén et al., 2005). Most of the studies of molybdenum exposure were carried out in experimental animals. In some studies, adult male rats, fed with sodium molybdate orally at the dose level of 10, 30, and 50 mg/kg body weight (5 days per week) for 60 days, showed a significant decrease in absolute and organ-to-body weight ratios of testes, epididymis, seminal vesicles, and ventral prostate. Sperm abnormality, associated with decrease in sperm motility and sperm count, was also observed. Significant alterations in activities of marker testicular enzymes, such as sorbitol dehydrogenase (decreased), LDH (increased) and gamma-glutamyl transpeptidase (increased) associated with histopathological changes in testes, was also observed. Accumulation of molybdenum in testes, epididymides, and seminal vesicles was also observed. The study revealed that the oral ingestion of molybdenum may affect the histoarchitecture of testes and sperm morphology (Pandey and Singh, 2002). In some other studies, when sodium molybdate was fed to two Holstein male calves, usual symptoms of molybdenum poisoning consisting of mild diarrhea, decreased body weight gains, anemia, and graying of the black hair areas were observed. The most striking and heretofore unnoted symptom was the lack of sexual interest or libido exhibited by these two animals. Histological examination of the testes showed marked damage to interstitial cells and germinal epithelium with little or no spermatogenesis present (Thomas and Moss, 1951).

Nickel

Nickel salts are considered an industrial health hazard, because many nickel compounds reach the human environment (Venugopal and Luckey, 1978), and exert potent toxic effects on peripheral tissues as well as on the reproductive system. Effects of nickel compounds on reproduction in rodent models are well documented (Pandey et al, 1999; Das and Dasgupta, 2000). Bioaccumulation of nickel in testis is well demonstrated, and the exact mechanisms of nickel-induced male reproductive toxic effects are mediated by various factors (Kakela et al, 1999; Obone et al, 1999). Low dietary protein, coupled with exposure to this metal, induces more severe changes, including biochemical defects, structural disorders, and altered physiologic functions.

Reports suggested nickel exposure causes decrease in weights of testicular and accessory sex organs and decrease in testicular steroidogenic enzymes activities (Δ^5 3β-HSD and 17β-HSD) (Das and Dasgupta, 2000). Some reports suggested high blood nickel levels have a significant positive correlation with morphologically abnormal sperm, together with sperm tail defects (Danadevi et al., 2003). Experiments in animals have shown testicular toxicity involving OS after high doses of nickel. This is evidenced by increased LPO, DNA damage, and apoptosis in the testes, morphological sperm head abnormalities, and decreased fertility in mice (Doreswamy et al., 2004), decreased DNA, RNA, and total protein in testes, and decreased sperm count and motility in rats (Das and Dasgupta, 2000), and decreased absolute and relative weights of testes, epididymides, seminal vesicles and prostate gland, decreased sperm count and motility, and increased abnormal sperm morphology in mice (Pandey et al., 1999). Other reports provide some evidence that nickel may be essential for male reproduction in rats (Nielsen et al., 2002; Yokoi et al., 2003).

However, as described by various reports, the basic mode of action of nickel-induced toxicity in male reproductive dysfunctions is evident by the involvement of OS mechanisms (Stinson et al, 1992; Chen et al 1998).

Selenium

Selenium is an essential trace mineral that is required for many physiological functions in animals, and the potential relevance of selenium to the reproductive system of livestock has been considered by many researchers. It is also an essential component of several major metabolic pathways, including thyroid hormone metabolism, antioxidant defense systems, and immune function (Brown and Arthur, 2001). In animals, selenium has been shown to be an essential element for healthy male reproductive

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

function. It has been reported to have both beneficial and adverse effects to male reproductive functions. It is essential for healthy spermatogenesis of mammals and its critical role is mainly mediated by two selenoproteins, namely, phospholipid hydroperoxide glutathione peroxidase (PHGPx/GPx4) and selenoprotein P. PHGPx/GPx4 is the major selenoprotein expressed by germ cells in the testis, having multiple functions and representing the pivotal link between selenium, sperm quality, and male fertility. Selenoprotein P is a plasma protein that is required for selenium supply to the testis (Boitani and Puglisi, 2008).

The best-characterized effect of selenium deficiency on mammalian spermatozoa is a loss of motility, breakage at the midpiece level, and an increased incidence of sperm-shape abnormalities, mostly of the sperm head (Wallace et al., 1983, Watanabe and Endo, 1991). In addition, the antioxidant enzyme, GPx, which has been assumed to play a role in protecting cells from the harmful effects of toxic metabolites and free radicals by preventing LPO of membranes (Alvarez and Storey, 1989), constitutes selenium as an essential component of it (Rotruck et al., 1973). It is also considered to be one of the most efficient protective agents against cadmium-induced injury.

On the contrary, selenium has long been known to have a damaging effect on different tissues of several species of animals. Some reports showed that selenium dioxide (SeO_2) has an adverse toxic effect on the testis (Roy Chowdhury and Bhatt, 1983). They showed both low and high concentrations of seminal plasma selenium may be harmful to male fertility (Bleau et al., 1984). Some repots showed intertubular edema, oligospermia, and scattered foci of degenerated spermatids were found after chronic exposure of the rat to selenium. In addition, marked inhibition in activities of testicular steroidogenic enzymes occurred, along with a significant reduction of mean tubular diameters, mean tubular areas, and mean tubular perimeters (Nebbia et al., 1987).

Silver

Silver is a naturally occurring precious metal, most often as a mineral ore in association with other elements. Reports regarding the effect of silver on male reproduction are rather scarce. Few earlier reports suggested the beneficial health effects of silver. They showed that silver, when used in reasonable amounts, has no negative effects on the human body and has a natural antimicrobial activity (Margaret et al., 2006; Sarkar et al., 2007). But, some other research works reported that silver exposure causes reduced activity of creatine kinase, an important enzyme that plays a major role in sperm energy homeostasis (Yesilli et al., 2005), possibly through the displacement of Mg^{+2} in this enzyme (Ghaffari and Motlagh, 2011). In addition, silver nanoparticles are shown to have severe toxic effects on the male reproductive system. The reports suggest that nanoparticles cross the blood-testes barrier and are deposited in the testes, and that there is potential for adverse effects on sperm cells (McAuliffe and Perry, 2007). Silver nanoparticles can bind to testicular tissues and can cause potential toxic effects, such as cell activation, producing reactive oxygen species (ROS), which are more toxic to tissue, inflammation, and, finally, all these processes gradually lead to cell death (Xia et al., 2006).

Vanadium

Vanadium has been recognized as an industrial hazard that adversely affects human and animal reproductive health. Because testicular function is exquisitely susceptible to ROS, some studies have elucidated the possible involvement of OS in vanadium-induced testicular toxicity (Llobet et al., 1993). They also reported on a significantly reduced sperm count associated with decreased serum testosterone and gonadotropin level in the vanadium-treated group of rats in the consequence of damaging effects of vanadium-induced ROS on developing germ cells and Sertoli cells (Fortoul et al., 2007). Some reports suggested that alterations on testicular gamma-tubulin might imply changes in microtubule-involved function, such as cell division, which, in the testes, might lead to damage in the spermatogenesis (Mussali-Galante et al., 2005). Vanadium has also been reported to cause adrenocortical hyperactivity, as evidenced by the elevated secretion of glucocorticoids, adrenal gland hypertrophy, and increased activity of adrenal $\Delta^5 3\beta$-HSD, along with increased testicular LPO (Uche et al., 2008).

Zinc

The relationship of zinc to morphologic, physiologic, and metabolic functions in the male reproductive system is well recognized. Semen and its constituents generally contain high levels of zinc, although concentrations vary among animals and species (Hidiroglou and Knipfel, 1984); the relationships between zinc and fertility of semen are unclear.

During zinc deficiency, retarded development of testicular growth involved marked atrophy of tubular epithelium and reduced DNA, RNA, and protein, as well as reduced zinc contents of testis, epididymis, and dorsolateral prostate (Hidiroglou and Knipfel, 1984). Studies have shown that oral zinc supplementation improves both sperm count (Carpino et al., 1998), motility (Kynaston et al., 1988), and the physical characteristics of sperm in some groups of infertile men (Tikkiwal et al., 1987). A preliminary trial found that zinc supplements (240 mg/day) increased sperm counts and possibly contributed to successful impregnation by 3 of the 11 men (Marmar et al., 1975). Omu et al. (1998) reported, in a controlled trial with 100 men, with low sperm motility, who received 57 mg of zinc twice-daily for 3 months, showed improvement in sperm quality, sperm count, sperm motility, and fertilizing capacity of sperm.

Functions of zinc in hormone interrelationships are little understood, but zinc deficiency decreases the output of pituitary gonadotrophins (e.g., LH and FSH) and androgen (e.g., testosterone) production, and zinc

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

turnover involves testosterone as well as pituitary hormones (Prasad et al., 1996). Metabolic regulation of sperm appears to be mediated through zinc as a regulator of enzyme activity in semen. Within spermatozoa, zinc is closely associated with –SH groups and disulfide linkages and is concentrated in the tail (Hidiroglou and Knipfel, 1984). Control of motility of sperm by zinc apparently involves control of energy utilization through adenosine triphosphate system involved in contraction and through regulation of phospholipid energy reserves (Riffo et al., 1992). The many roles for zinc in the male reproductive system are extremely complex and scarcely understood. The importance of zinc contents of commonly utilized feedstuffs in relation to reproductive capabilities of the mammalian sperm remain unclear, although zinc deficiency in relation to male reproduction may be much more widespread than is recognized commonly.

Conclusions

Findings from different scientific studies indicated that the degree of toxic manifestation of different metals depends on dose, duration, route of administration, and other physiological factors, especially nutrition. Toxic manifestation by different metals varies from species to species. The signs and symptoms of metal toxicity depend on the duration of exposure, type of metal, condition of workplace, socioeconomic status, and history of disease. But, extensive literature study has explored that there is a gap of knowledge in the proper toxicity survey. Current ongoing trials will provide answers on the safety and effectiveness of exposure of these metals, and further efforts should be made to widen our knowledge in this unmapped area of research.

Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of this paper.

References

Acharya, U., Mowen, M. B., Nagashima, K., Acharya, J. K. (2004). Ceramidase expression facilitates membrane turnover and endocytosis of rhodopsin in photoreceptors. Proc Natl Acad Sci,U S A 101:1922–1926.

Agrawal, R., Chansouria, J. P. (1989). Chronic effects of mercuric chloride ingestion on rat adrenocortical function. Bull Environ Contam Toxicol 43:481–84.

Alcser, K. H., Brix, K. A., Fine, L. J., Kallenbach, L. R., Wolfe, R. A. (1989). Occupational mercury exposure and male reproductive health. Am J Ind Med 15:517–529.

Alexander, B. H., Checkoway, H., van Netten, C., Muller, C. H., Ewers, T. H., Kaufman, J. D., et al. (1996). Semen quality of men employed at a lead smelter. Occup Environ Med 53:411–416.

Alvarez, J. G., Storey, B. T. (1989). Role of glutathione peroxidase in protecting mammalian spermatozoa from loss of motility caused by spontaneous lipid peroxidation. Gamete Res 23:77–90.

Apostoli, P., Bellini, A., Porru, S., Bisante, L. (2000). The effect of lead on male fertility: a time to pregnancy (TTP) study. Am J Ind Med 38:310–315.

Apostoli, P., Kiss, P., Porru, S., Bonde, J. P., Vanhoorne, M. (1998). Male reproductive toxicity of lead in animals and humans. Occup Environ Med 55:364–374.

Armstrong, C. W., Moore, L. W., Jr., Hackler, R. L., Miller, G. B., Jr., Stroube, R. B. (1983). An outbreak of metal fume fever. Diagnostic use of urinary copper and zinc determinations. J Occup Med 25:886–888.

Aruldhas, M. M., Subramanian, S., Sekhar, P., Hasan, G. C., Govindarajulu, P., Akbarsha, M. A. (2004). Microcanalization in the epididymis to overcome ductal obstruction caused due to chronic exposure to chromium—a study in mature bonnet monkey (Macaca radiata Geoffroy). Reproduction 128:127–137.

Bagchi, D., Stohs, S. J., Downs, B. W., Bagchi, M., Preuss, H. G. (2002). Cytotoxicity and oxidative mechanisms of different forms of chromium. Toxicology 180:5–22.

Barber, S. J., Parker, H. M., McDaniel, C. D. (2005). Broiler breeder semen quality as affected by trace minerals in vitro. Poult Sci 84:100–105.

Barceloux, D. (1999). Chromium. Clin Toxicol 37:173–194.

Barregärd, L., Lindstedt, G., Schütz, A., Sällsten, G. (1994). Endocrine function in mercury exposed chloralkali workers. Occup Environ Med 51:536–540.

Batra, N., Nehru, B., Bansal, M. P. (1998). The effect of zinc supplementation on the effects of lead on the rat testis. Reprod Toxicol 12:535–540.

Becker, D. E., Smith, S. E. (1951). The level of cobalt tolerance in yearling sheeps. J Anim Sci 10:266–271.

Benoff, S., Centola, G. M., Millan, C., Napolitano, B., Marmar, J. L., Hurley, I. R. (2003). Increased seminal plasma lead levels adversely affect the fertility potential of sperm in IVF. Hum Reprod 18:374–383.

Benoff, S., Hurley, I. R., Barcia, M., Mandel, F. S., Cooper, G. W., Hershlag, A. (1997). A potential role for cadmium in the etiology of varicocele-associated infertility. Fertil Steril 67:336–347.

Biswas, R., Poddar, S., Mukherjee, A. (2006). Investigation on the genotoxic effects of long-term administration of sodium arsenite in bone marrow and testicular cell in vivo using comet assay. J Environ Pathol Toxicol Oncol 26:29–37.

Bleau, G., Lemarbre, J., Faucher, G., Roberts, K. D., Chapdelaine, A. (1984). Semen selenium and human fertility. Fertil Steril 42:890–894.

Boitani, C., Puglisi, R. (2008). Selenium, a key element in spermatogenesis and male fertility. Adv Exp Med Biol 636:65–73.

Bomhard, E., Vogel, O., Loser, E. (1987). Chronic effects on single and multiple oral and subcutaneous cadmium administration on the testes of Wistar rats. Cancer Lett 36:307–315.

Bondani, A., Aspeitia, E., Aznar, R., Gómez-Arzápalo, E., Pascual, C., Giner, J. (1973). Co-relation between sperm motility and electrolyte composition of seminal fluid in normal and infertile men. Fertil Steril 24:150–158.

Bonde, J. P. (1993). The risk of male subfertility attributable to welding of metals. Studies of semen quality, infertility, adverse pregnancy outcome and childhood malignancy. Int J Androl 16:1–29.

Bonde, J. P. (2002). Occupational risk to male reproduction. G Ital Med Lav Ergon 24:112–117.

Brown, K. M., Arthur, J. R. (2001). Selenium, selenoproteins and human health: a review. Pub Health Nutr 4:593–599.

Brown, A. E. (1999). Pesticides and the endocrine system. College Park: Department of Entomology, University of Maryland; Pesticide Information Leaflet Series, 34.

Campanella, L., Gatta, T., Ravera O. (2005). Relationship between antioxidant capacity and manganese accumulation in the soft tissues of two freshwater molluscs: Unio pictorum mancus (Lamellibranchia, Unionidae) and Viviparous ater (Gastropoda, Prosobranchia). J Limnol 64:153–158.

Canpolat, I., Gur, S., Gunay, C., Bulut, S., Eroksuz, H. (2006). An evaluation of the outcome of bull castration by itra-testicular

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

injection of ethanol and calcium chloride. Revue Med Vet 157:420–425.
Carpino, A., Siciliano, L., Petroni, M. F., De Stefano, C., Aquila, S., Andó, S. (1998). Low seminal zinc bound to high molecular weight proteins in asthenozoospermic patients: evidence of increased sperm zinc content in oligoasthenozoospermic patients. Hum Reprod 13:111–114.
Cavallini, L., Valente, M., Bindoli, A. (1984). On the mechanism of inhibition of lipid peroxidation by manganese. Inorganica Chim Acta 91:117–120.
Chandra, A., Goswami, H., Sengupta, P. (2012a). Dietary calcium induced cytological and biochemical changes in thyroid. Environ Toxicol Pharmacol 34:454–465.
Chandra, A., Sengupta, P., Goswami, H., Sarkar, M. (2012b). Excessive dietary calcium in the disruption of structural and functional status of adult male reproductive system in rat with possible mechanism. Mol Cell Biochem 364:181–191.
Chandra, A., Sengupta, P., Goswami, H., Sarkar, M. (2012c). Effects of dietary magnesium on testicular histology, steroidogenesis, spermatogenesis and oxidative stress markers in adult rats. Ind J Exp Biol (in press).
Chandra, S. V., Ara, R., Nagar, N., Seth, P. K. (1973). Sterility in experimental manganese toxicity. Acta Biol Med Ger 30:857–862.
Chang, S. I., Jin, B., Youn, P., Park, C., Park, J. D., Ryu, D. Y. (2007). Arsenic induced toxicity and the protective role of ascorbic acid in mouse testis. Toxicol Appl Pharmacol 218:196–203.
Chaplin, R. E., Harris, M. W., Hunter, E. S., Davis, B. J., Collins, B. J., Lockhart, A. C. (1995). The reproductive and developmental toxicity of Indium in the swiss mouse. Toxicol Sci 27:140–148.
Chattopadhyay, A., Sarkar, M., Biswas, N. M. (2005). Dose dependant effect of copper chloride on male reproductive function in immature rats. Kathmandu Univ Med J 3:392–400.
Chen, C. Y., Huang, Y. L., Lin, T. H. (1998). Association between oxidative stress and cytokine production in nickel-treated rats. Arch Biochem Biophys 356:127–132.
Cheng, C. Y., Wong, E. W. P., Lie, P. P. Y., Li, M. W. M., Su, L., Siu, E. R., et al. (2011). Environmental toxicants and amle reproductive function. Spermatogenesis 1:2–13.
Chia, S. E., Ong, C. N., Lee, S. T., Tsakok, F. H. (1992). Blood concentrations of lead, mercury, zinc, and copper, and human semen parameters. Arch Androl 29:177–183.
Chia, S. E., Xu, B., Ong, C. N., Tsakok, F. M., Lee, S. T. (1994). Effect of cadmium and cigarette smoking on human semen quality. Int J Fertil Menopausal Stud 39:292–298.
Chowdhury, A. R., Mitra, C. (1995). Spermatogenic and steroidogenic impairment after chromium treatment in rats. Ind J Exp Biol 33:480–484.
Chowdhury, A. R., Arora, U. (1982). Toxic effect of mercury on testes in different animal species. Ind J Physiol Pharmacol 26:246–249.
Coassin, M., Ursini, F., Bindoli, A. (1992). Antioxidant effect of manganese. Arch Biochem Biophys 299:330–333.
Cordier, S., Deplan, F., Mandereau, L., Hemon, D. (1991). Paternal exposure to mercury and spontaneous abortions. Br J Ind Med 48:375–381.
Danadevi, K., Rozati, R., Reddy, P. P., Grover, P. (2003). Semen quality of Indian welders occupationally exposed to nickel and chromium. Reprod Toxicol 17:451–456.
Darmani, H., Al-Hiyasat, A. S., Elbetieha, A. M. (2001). Effects of sodium fluoride in drinking water on fertility in female mice. Fluoride 34:242–249.
Das, K. K., Dasgupta, S. (2000). Effect of nickel on testicular nucleic acid concentrations of rats on protein restriction. Biol Trace Elem Res 73:175–180.
Dickinson, H., Parker, L. (1994). Do alcohol and lead change the sex ratio? J Theor Biol 169:313–315.
Dickman, M. D., Leung, K. M. C., Koo, L. C. L. (1999). Mercury in human hair and fish: is there a Hong Kong male subfertility connection? Marine Pollut Bull 39:352–356.
Doreswamy, C., Govindan, R., Devaiah, M. C., Muniswamappa, M. V. (2004). Deterioration of cocoon traits of silkworm, Bombyx mori L. by the synergistic infection with late larval flacherie pathogens. Karnataka J Agric Sci 17:345–348.
Duffus, J. H. (2002). Effect of CrVI on sperm quality. Ann Occup Hyg 46:269–270.
Eidi, M., Eidi, A., Pouyan, O., Shahmohammadi, P., Fazaeli, R., Bahar, M. (2010). Seminal plasma level of copper and its relationship with seminal parameters. Ira J Repro Med 8:60–65.
Elbetieha, A. M., Darmani, H., Al-Hiyasat, A. S. (2000). Fertility effects of sodium fluoride in male mice. Fluoride 33:128–134.
Emara, A. M., el-Ghawabi, S. H., Madkour, O. I., el-Samra, G. H. (1971). Chronic manganese poisoning in the dry battery industry. Br J Ind Med 28:78–82.
Erfurth, E. M., Gerhardsson, L., Nilsson, A., Rylander, L., Schütz, A., Skerfving, S., et al. (2001). Effects of lead on the endocrine system in lead smelter workers. Arch Environ Health 56:449–455.
Ernst, E. (1990). Testicular toxicity following short-term exposure to tri-and hexavalent chromium: an experimental study in the rat. Toxicol Lett 51:269–275.
Ernst, E., Bonde, J. P. (1992). Sex and epididymal sperm parameters in rat following subchronic treatment with hexavalent chromium. Hum Environ Toxicol 11:255–258.
Espinoza-Navarro, O., Vilaxa, A., Granifo, L., Rojas, S., Rodríguez, H. (2007). Histological study on the male reproductive organs of mouse CF1 treated with boron. Int J Morphol 25:341–346.
Fisher-Fischbein, J., Fischbein, A., Melnick, H. D., Bardin, C. W. (1987). Correlation between biochemical indicators of lead exposure and semen quality in a lead-poisoned firearms instructor. JAMA 257:803–805.
Fortoul, T. I., Bizarro-Nevares, P., Acevedo-Nava, S., Piñón-Zárate, G., Rodríguez-Lara, V., Colín-Barenque, L., et al. (2007). Ultrastructural findings in murine seminiferous tubules as a consequence of subchronic vanadium pentoxide inhalation. Reprod Toxicol 23:588–592.
Friedmann, A. S., Chen, H. L., Rabuck, L. D., Zirkin, B. R. (1998). Accumulation of dietary methylmercury in the testes of the adult brown norway rat: impaired testicular and epididymal function. Environ Toxicol Chem 17:867–871.
Ghaffari, M. A., Motlagh, B. (2011). In vitro effect of lead, silver, tin, mercury, indium, and bismuthon human sperm creatine kinase activity: a presumable mechanism for men infertility. Iranian Biomed J 15:38–42.
Godatvar, P. R. Shukra: a clinical and experimental study on therole of Svarna Bhasma in Normozoospermia. Jamnagar: MD thesis submitted to Gujrat Ayurved University, 1995.
Hamadouche, A., Slimani, M., Merad-Boudia, B., Zaoui, C. (2009). Reproductive toxicity of lead acetate in adult male rats. Am J Sci Res 3:38–50..
Hanf, V., Forstmann, A., Costea, J. E., Schieferstein, G., Fischer, I., Schweinsberg, F. (1996). Mercury in urine and ejaculate in husbands of barren couples. Toxicol Lett 88:227–231.
Hidiroglou, M., Knipfel, J. E. (1984). Zinc in mammalian sperm: a review. J Dairy Sci 67:1147–1156.
Hui, C. A. (2002). Concentrations of chromium, manganese and lead in air and avian eggs. Env Poll 120:201–206.
Jana, K., Jana, S., Samanta, P. K. (2006). Effects of chronic exposure to sodium arsenite on hypothalamo-pituitary-testicular activities in adult rats: possible an estrogenic mode of action. Reprod Biol Endocrinol 4:1–13.
Jana, K., Samanta, P. K. (2006). Evaluation of single intratesticular injection of calcium chloride for nonsurgical sterilization in adult albino rats. Contraception 73:289–300.
Jain, V., Rai, A., Misra, S., Singh, K. M. (2010). Seminal gold content in healthy fertile men in India. Int J Ayur Res 1:172–174.
Joffe, M., Bisanti, L., Apostoli, P., Kiss, P., Dale, A., Roeleveld Lindbohm, M. L., et al. (2003). Time to pregnancy and occupational lead exposure. Occup Environ Med 60:752–758.

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

Jones, M. M., Xu, C., Ladd, P. A. (1997). Selenite suppression of cadmium-induced testicular apoptosis. Toxicology 116:169–75.
Jurasovíc, J., Cvitković, P., Pizent, A., Colak, B., Telisman, S. (2004). Semen quality and reproductive endocrine function with regard to blood cadmium in Croatian male subjects. Biometals 17:735–743.
Kakela, R., Kakela, A., Hyvarinen, H. (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.
Kumar, G. P., Laloraya, M., Laloraya, M. M. (1990). Powerful anti-sperm motility action of cobaltous ion and its recovery by a sulfhydryl compound. Contraception 41:633–639.
Kynaston, H. G., Lewis-Jones, D. I., Lynch, R. V., Desmond, A. D. (1988). Changes in seminal quality following oral zinc therapy. Andrologia 20:21–22.
Laskey, J. W., Rehnberg, G. L., Hein, J. F., Carter, S. D. (1982). Effects of chronic manganese (Mn3O4) exposure on selected reproductive parameters in rats. J Toxicol Environ Health 9:677–687.
Lauwerys, R, Lison, D. (1994). Health risks associated with cobalt exposure—an overview. Sci Total Environ 150:1–6.
Lauwerys, R., Roels, H., Genet, P., Toussaint, G., Bouckaert, A., De Cooman, S. (1985). Fertility of male workers exposed to mercury vapor or to manganese dust: a questionnaire study. Am J Ind Med 7:171–176.
Lee, I. P., Dixon, R. L. (1975). Effects of mercury on spermatogenesis studied by velocity sedimentation cell separation and serial mating. J Pharmacol Exp Ther 194:171–181.
Lerda, D. (1992). Study of sperm characteristics in persons occupationally exposed to lead. Am J Ind Med 22:567–571.
Leung, T. Y., Choy, C. M. Y., Yim, S. F., Lam, C. W., Haines, C. J. (2001). Whole blood mercury concentrations in sub-fertile men in Hong Kong. Aust N Z J Obstet Gynaecol 41:75–77.
Levina, A., Codd, R., Dillon, C. T., Lay, P. A. (2003). Chromium in biology: toxicology and nutritional aspects. Prog Inorg Chem 51:145–250.
Li, H., Chen, Q., Li, S., Yao, W., Li, L., Shi, X., et al. (2001). Effect of CrVI exposure on sperm quality: human and animal studies. Ann Occup Hyg 45:505–511.
Lin, Y. S., Caffrey, J. L., Chang, M. H., Dowling, N., Lin, J. W. (2010). Cigarette smoking, cadmium exposure, and zinc intake on obstructive lung disorder. Respir Res 11:53–60.
Lin, S., Hwang, S. A., Marshall, E. G., Stone, R., Chen, J. (1996). Fertility rates among lead workers and professional bus drivers: a comparative study. Ann Epidemiol 6:201–208.
Lindbohm, M. L., Sallmén, M., Anttila, A., Taskinen, H., Hemminki, K. (1991). Paternal occupational lead exposure and spontaneous abortion. Scand J Work Environ Health 17:95–103.
Llobet, J. M., Colomina, M. T., Sirvent, J. J., Doningo, J. L., Corbella, J. (1993). Reproductive toxicity evaluation of vanadium in male mice. Toxicology 80:199–206.
Long, H., Jin, Y., Lin, M., Sun, Y., Zhang, L., Clinch, C. (2009). Fluoride toxicity in male reproductive system. Fluoride 42:260–276.
Lotrich, F. E., Smith, G. S., Pollock, B. G. (2006). Relevance of assessing drug concentration exposure in pharmacogenetic and imaging studies. J Psychopharmacol 4:33–40.
Lymberopoulos, A. G., Kotsaki-Kovatsi, V. P., Papaioannou, N., Taylor, A., Brikas, P., Belibasaki, S. (2003). Effects of cadmium chloride administration on the testicular growth and plasma testosterone secretion of Chios ram-lambs. Small Rum Res 49:51–60.
Madzharova, M., Gluhcheva, Y., Atanassova, P. N. (2010). Effect of cobalt on male reproductive organs during puberty. Biotech Biotech Equip 24:321–324.
Margaret, I. P., Lui, S. L., Poon, V. K. M., Lung, I., Burd, A. (2006). Antimicrobial activities of silver dressings: an in vitro comparison. J Med Microbiol 55:59–63.
Marmar, J. L., Katz, S., Praiss, D. E., DeBenedictis, T. J. (1975). Semen zinc levels in infertile and postvasectomy patients and patients with prostatitis. Fertil Steril 26:1057–1063.
McAuliffe, M. E., Perry, M. J. (2007). Are nanoparticles potential male reproductive toxicants? A literature review. Nanotoxicology 1:204–210.
McGregor, A. J., Mason, H. J. (1991). Occupational mercury vapour exposure and testicular, pituitary and thyroid endocrine function. Hum Exp Toxicol 10:199–203.
Mena, I., Marin, O., Fuenzalida, S., Papavasiliou, P. S., Cotzias, G. C. (1967). Modification of chronic manganese poisoning. Treatment with L-dopa or 5-OH tryptophane. Neurology 17:128–136.
Min, Y. I., Correa-Villaseiior, A., Stewart, P. A. (1996). Parental occupational lead exposure and low birth weight. Am J Ind Med 30:569–578.
Mohamed, M. K., Burbacher, T. M., Mottet, N. K. (1987). Effects of methyl mercury on testicular functions in Macaca fascicularis monkeys. Pharmacol Toxicol 60:29–36.
Moorman, W. J., Skaggs, S. R., Clark, J. C., Turner, T. W., Sharpnack, D. D., Murrell, J. A., et al. (1998). Male reproductive effects of lead, including species extrapolation for the rabbit model. Reprod Toxicol 12:333–346.
Mussali-Galante, P., Rodríguez-Lara, V., Hernández-Tellez, B., Avila-Costa, M. R., Colín-Barenque, L., Bizarro-Nevarez, P., et al. (2005). Inhaled vanadium pentoxide decrease gamma-tubulin of mouse testes at different exposure times. Toxicol Ind Health 21:215–222.
Nebbia, C., Brando, C., Burdino, E., Rasero, R., Valenza, F., Arisio, R., et al. (1987). Effects of the chronic administration of sodium selenite on rat testes. Res Commun Chem Pathol Pharmacol 58:183–197.
Neiger, R. D., Osweiler, G. D. (1985). Effect of subacute lowlevel dietary sodium arsenite on dogs. Fundam Appl Toxicol 13:439–451.
Nielsen, P. H., Roslev, P., Ducholm, T., Nielsen, J. L. (200). Microthrix parvicella, a specialized lipid consumer in anaerobic-aerobic activated sludge plants. Water Sci Tech 46:73–80.
Nordberg, G. F., Fowler, B. A., Nordberg, M., Friberg, L. (2005). Handbook on the toxicology of metals, 3rd ed. Copenhagen: European Environment Agency, Academic Publishers.
Nordberg, G. F., Piscator, M., Nordberg, M. (1971). On the distribution of cadmium in blood. Acta Pharmacol Toxicol 30:289–295.
Obone, E., Chakrabarti, S. K., Bai, C., Malick, M. A., Lamontagne, L., Subramanian, K. S. (1999). Toxicity and bioaccumulation of nickel sulfate in Sprague-Dawley rats following 13 weeks of subchronic exposure. J Toxicol Environ Health A 57:379–401.
Omu, A. E., Dashti, H., Al-Othman, S. (1998). Treatment of asthenozoospermia with zinc sulphate: andrological, immunological, and obstetric outcome. Eur J Obstet Gynecol Reprod Biol 79:179–184.
Omura, M., Koji, Y., Akiyo, T., Miyuki, H., Yuji, M., Naohide, I. (2000). Changes in testicular damage caused by indium arsenide and indium phosphide in hampsters during two years after intratracheal instillations. J Occup Health 42:196–204.
Omura, M., Tanaka, A., Hirata, M., Inoue, N., Ueno, T., Homma, T., et al. (2002). Testicular toxicity evaluation of indium-tin oxide. J Occup Health 44:105–110.
Orisakwe, O. E., Afonne, O. J., Nwobodo, E., Asomugha, L., Dioka, C. E. (2001). Low-dose mercury induces testicular damage protected by zinc in mice. Eur J Obstet Gynecol Reprod Biol 95:92–96.
Oser, B. K. (1975). Hawk's physiological chemistry (pp. 561–568). New York: McGraw-Hill.
Pandey, R., Kumar, R., Singh, S. P., Saxena, D. K., Srivastava, S. P. (1999). Male reproductive effect of nickel sulphate in mice. Biometals 12:339–346.
Pandey, R., Singh, S. P. (2002). Effects of molybdenum on fertility of male rats. Biometals 15:65–72.
Pant, N., Kumar, R., Murthy, R. C., Srivastava, S. P. (2001). Male reproductive effect of arsenic in mice. Biometals 14:113–117.
Pant, N., Murthy, R. C., Srivastava, S. P. (2004). Male reproductive toxicity of sodium arsenite in mice. Hum Exp Toxicol 23:399–403.
Pedersen, L. H., Stoltenberg, M., Ernst, E., West, M. J. (2003). Leydig cell death in rats exposed to bismuth subnitrate. J Appl Toxicol 23:235–238.
Pedigo, N. G., George, W. J., Anderson, M. B. (1988). Effect of acute and chronic exposure of cobalt on male reproduction in mice. Reprod Toxicol 2:45–53.

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK

Ponnapakkam, T. P., Bailey, K. S., Graves, K. A., Iszard, M. B. (2003). Assessment of male reproductive system in the CD-1 mice following oral manganese exposure. Reprod Toxicol 17:547–551.

Prasad, A. S., Mantzoros, C. S., Beck, F. W., Hess, J. W., Brewer, G. J. (1996). Zinc status and serum testosterone levels in healthy adults. Nutrition 12:344–348.

Queiroz, E. K. R., Waissmann, W. (2006). Occupational exposure and effects on the male reproductive system. Cad Saúde Pública 22:485–493.

Quintanilla-Vega, B., Hoover, D., Bal, W., Silbergeld, E. K., Waalkes, M. P., Anderson, L. D. (2000). Lead effects on protamine-DNA binding. Am J Ind Med 38:324–329.

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

Riffo, M., Leiva, S., Astudillo, J. (1992). Effect of zinc on human sperm motility and the acrosome reaction. Int J Androl 15:229–237.

Robbins, W. A., Wei, F., Elashoff, D. A., Wu, G., Xun, L., Jia, A. J. (2007). Y:X sperm ration in boron exposed men. J Androl 29:115–121.

Rodier, J. (1955). Manganese poisoning in Moroccan miners. Br J Ind Med 12:21–35.

Rotruck, J. T., Pope, A. L., Ganther, H. E., Swanson, A. B., Hafeman, D. G., Hoekstra, W. G. (1973). Selenium: biochemical role as a component of glutathione peroxidase. Science 179:588–590.

Roy Chowdhury, A. (2009). Recent advances in heavy metal induced effect of male reproductive function. Al Ameen J Med Sci 2:37–42.

Roy Chowdhury, A., Bhatt, H. V. (1983). Effect of selenium dioxide on the testes of rat. Ind J Physiol Pharmacol 27:237–240.

Sallmén, M., Lindbohm, M. L., Anntila, A., Taskinen, H., Hemminki, K. (1992). Paternal occupational lead exposure and congenital malformations. J Epidemiol Comm Health 46:519–522.

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

Sarkar, S., Jana, A. D., Samanta, S. K., Mostafa, G. (2007). Facile synthesis of silver nano particles with highly efficient anti-microbial property. Polyhedron 26:4419–4426.

Saxena, D. K., Murthy, R. C., Singh, C., Chandra, S. V. (1989). Zinc protects testicular injury induced by concurrent exposure to cadmium and lead in rats. Res Commun Chem Pathol Pharmacol 64:317–329.

Saygi, S., Deniz, G., Kutsal, O., Vural, N. (1991). Chronic effects of cadmium on kidney, liver, testis, and fertility of male rats. Biol Trace Elem Res 31:209–214.

Scialli, A. R., Bonde, J. P., Brüske-Hohlfeld, I., Culver, B. D., Li, Y., Sullivan, F. M. (2010). An overview of male reproductive studies of boron with an emphasis on studies of highly exposed Chinese workers. Reprod Toxicol 29:10–24.

Seldén, A. I., Berg, N. P., Soderbergh, A., Bergstrom, E. O. (2005). Occupational molybdenum exposure and a gouty electrician. Occup Med 55:145–148.

Sengupta, P., Chandra, A. (2009). Potentializing the effect of excess dietary calcium chloride as chemo-castrative agent. International Conference of Integrated Physiology: Modern Perspective and Platinum Jubilee Celebration, November 12–14, 2009, Kolkata, India, p. 277.

Sengupta, P. (2011a). A scientific review of age determination for a laboratory rat: how old is it in comparison with human age? Biomed Int (in press).

Sengupta, P., Sarkar, M., Chandra, A. (2011b). Excess dietary calcium depresses male gonadal activity by inducing oxidative stress in adult albino rats. 98th Indian Science Congress, January 3–7, 2011, Chennai, India, p. 193.

Sengupta, P., Sarkar, M., Chandra, A. (2011c). Comparative study of calcium and magnesium induced oxidative stress leading to gonadal impairment in male rats. National Symposium on "Frontiers in Modern Biology" organized by Department of Biological Sciences, p. 18.

Sengupta, P., Goswami, H., Chandra, A. (2011d). Excessive magnesium intake reduces testicular oxidative stress and promotes male reproductive function in rats. Physicon 2011:115.

Sengupta, P. (2012). Health impacts of yoga and pranayama: A state-of-the-art review. Int J Prev Med 3: 444-458.

Seth, P. K., Nagar, N., Husain, R., Chandra, S. V. (1973). Effects of manganese on rabbit testes. Environ Physiol Biochem 3:263–267.

Sharma, S., Haridatta, V., Shastri, K. (Eds.). (1979). Suvarna Guna- Suvarna Vigyanam-25 /69–70, Rasa Tarangini,. 11th ed. (pp. 375–376). Delhi: Motilal Banarasidas Delhi.

Shiau, C. Y., Wang, J. D., Chen, P. C. (2004). Decreased fecundity among male lead workers. Occup Environ Med 61:915–923.

Shrinivas, P. (1998). A clinical study on the role of svarna bhasma and vajeekara drugs in the management of sukra dushti. Jamnagar: MD thesis submitted to Gujrat Ayurved University.

Sinclair, S. (2000). Male infertility: nutritional and environmental considerations. Altern Med Rev 5:28–38.

Singh, P., Chand, D., Georgie, G. C. (1989). Effect of vitamin E on lipid peroxidation in buffalo Bubalus bubalis. Ind J Exp Biol 27:14–16.

Sipowicz, M. A., Anderson, L. M., Utermahlen, W. E., Jr., Issaq, H. J., Kasprzak, K. S. (1997). Uptake and tissue distribution of chromium (III) in mice after a single intraperitoneal or subcutaneous administration. Toxicol Lett 93:9–14.

Skandhan, K. P. (1981). Gold in human semen. Androlgia 18:78–82.

Skandhan, K. P. (1992). Review on copper in male reproduction and contraception. Rev Fr Gynecol Obstet 87:594–598.

Stinson, T. J., Jaw, S., Jeffery, E. H., Plewa, M. J. (1992). The relationship between nickel chloride-induced peroxidation and DNA strand breakage in rat liver. Toxicol Appl Pharmacol 117:98–103.

Stoltenberg, M., Flyvbjerg, A., Søndergaard, L. G., Rungby, J. (2002). Decreased serum testosterone levels in rats exposed intraperitoneally to bismuth subnitrate. J Appl Toxicol 22:111–115.

Sutherland, J. E., Zhitkovich, A., Kluz, T., Costa, M. (2000). Rats retain chromium in testis following chronic ingestion of drinking water containing hexavalent chromium. Biol Trace Elem Res 74:41–53.

Telišman, S., Cvitkovíc, P., Jurasovíc, J., Pizent, A., Gavella, M., Rocíc, B. (2000). Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect 108:45–53.

Thaker, A. (2000). The role of svarna Bhasma and Kokilaksha in the management of Ksheena Sukra (Oligozoospermia) Jamnagar: PhD thesis submitted to Gujrat Ayurved University.

Thomas, J. W., Moss, S. (1951). The effect of orally administered molybdenum on growth, spermatogenesis, and testes histology of young dairy bulls. J Dairy Sci 34:929–934.

Tikkiwal, M., Ajmera, R. L., Mathur, N. K. (1987). Effect of zinc administration on seminal zinc and fertility of oligospermic males. Ind J Physiol Pharmacol 31:30–34.

Tripathi, V. I. (1998). Shrimada vagbhatacharya virachit rasaratna samucchyaa Savimarsha Rasaprabha hindi vyakhya. In: Giri, K. D. (Ed.), Arshrogadhikara/9, 10, 1st ed. (p. 172). Varanasi, India: Chaukhamba Sanskrit Bhavan.

Uche, F. I., Obianime, A. W., Gogo-Abite, M. (2008). Effects of vanadium pentoxide on the histological and sperm parameters of male guinea pigs. J Appl Sci Environ Manag 12:107–115

Venugopal, B., Luckey, T. D. (1978). Metal toxicity in mammals (vol 2, pp. 289–297). New York: Plenum.

Viskum, S., Rabjerg, L., Jørgensen, P. J., Grandjean, P. (1999). Improvement in semen quality associated with decreasing occupational lead exposure. Am J Ind Med 35:257–263.

Waalkes, M. P., Rehm, S. (1994). Cadmium and prostate cancer. J Toxicol Environ Health 43:251–269.

Waissmann, W. (2002). Health surveillance and endocrine disruptors. Cad Saúde Pública 18:511–517.

Wallace, E., Cooper, G. W., Calvin, H. I. (1983). Effects of selenium deficiency on the shape and arrangement of rodent sperm mitochondria. Gamete Res 4:389–399.

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

© 2012 Informa Healthcare USA, Inc.

RIGHTSLINK

Watanabe, T., Endo, A. (1991) Effects of selenium deficiency on sperm morphology and spermatocyte chromosomes in mice. Mutat Res 262:93–99.

Wildt, K., Eliasson, R., Berlin, M. (1983). Effects of occupational exposure to lead on sperm and semen. In: Clarkson, T. W., Nordberg, G. F., Sager, P.R. (Eds.), Reproductive and developmental toxicity of metals (pp. 279–300). New York: Plenum.

Wirth, J. J., Rossano, M. G., Daly, D. C., Paneth, N., Puscheck, E., Potter, R. C., et al. (2007). Ambient manganese exposure is negatively associated with human sperm motility and concentration. Epidemiology 18:270–273.

Working, P. K. (1988). Male reproductive toxicology: comparison of the human to animal models. Environ Health Perspect 77:37–44.

Xia, T., Kovochich, M., Brant, J., Hotze, M., Sempf, J., Oberley, T., et al. (2006). Comparison of the abilities of ambient and manufactured nanoparticles to induce cellular toxicity according to an oxidative stress paradigm. Nano Lett 8:1794–1807.

Xu, D. X., Shen, H. M., Zhu, Q. X., Chua, L., Wang, Q. N., Chia, S. E., et al. (2003). The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead, and selenium in seminal plasma. Mutat Res 534:155–163.

Yang, C. Y. (1998). Calcium and magnesium in drinking water and risk of death from cerebrovascular disease. Stroke 29:411–414.

Yesilli, C., Mungan, G., Seckiner, I., Akduman, B., Acikgoz, S., Altan, K., et al. (2005). Effect of varicocelectomy on sperm creatin kinase, HspA2 chaperone protein (creatine kinase-M type), LDH, LDH-X, and lipid peroxidation product levels in infertile men with varicocele. Urology 66:610–615.

Yokoi, K., Uthus, E. O., Nielsen, F. H. (2003). Nickel deficiency diminishes sperm quality and movement in rats. Biol Trace Element Res 93:141–153.

Zeng, X., Jin, T., Jiang, X., Kong, Q., Ye, T., Nordberg, G. F. (2004). Effects on the prostate of environmental cadmium exposure. Biometals 17:559–566.

Zeng, X., Jin, T., Zhou, Y., Kong, Q. (2002). Alterations of serum hormone levels in male workers occupationally exposed to cadmium. J Toxicol Environ Health A 65:513–521.

Drug and Chemical Toxicology Downloaded from informahealthcare.com by 117.194.128.234 on 09/05/12
For personal use only.

RIGHTSLINK