Cadmium (Cd) is a potentially toxic to both humans and animals. Since, it does not have any detectable nutritional role in the biological system and because of its cumulative nature; its consumption even at the lower levels may affect the performance of animals in terms of production as well as immunity. Excess levels of Cd not only affect the animals health but, it adversely affect human health through consumption of meat/dairy product from these animals as some quantity of Cd is stored in edible tissues or secreted through milk. The present review focuses on the detailed overview of general perspective of Cd and its effect on hemato-biochemical parameters, immunity and oxidative stress indices.

**Key words:** Cadmium, immunity, milk, oxidative stress

Pollution and industrial practices result in an increase of toxic element concentrations in soil, atmosphere, feed, and water. Cd is considered one of the most abundant toxic substances in the environment because of its wide range of organ toxicity, lack of an effective homeostatic control mechanism in the body, and a long biological half-life of 10-30 yr (Jarup et al., 1998). The primary route of exposure to Cd occurs via contaminated drinking water or feed. Because the body has no mechanism for the excretion of Cd, Cd accumulates in tissues. Ingested Cd is deposited mainly in the kidneys and liver, followed by pancreas, bone, lungs, and placenta. Kidney is the target organ for long-term exposure (Jurczuk et al., 2004). Most Cd in the body is bound primarily to a heat-resistant, low-molecular-weight protein with a high cysteine content termed metallothionein, which functions in the homeostasis of essential metals such as zinc and copper (Lisic et al., 1996). Cd is known to disturb the oxidative status of the body and this is believed to underlie the adverse health effects of this metal. To prevent Cd-induced peroxidative tissue damage, there are protective mechanisms in vivo, such as an enzymatic defense system (antioxidant enzymes) and free-radical scavengers (antioxidants).

**Physical and Chemical Properties of Cadmium**

Cd is an element with the symbol Cd and atomic number 48 with an atomic weight 112.4. Cd is a soft, malleable, ductile, bluish-white bivalent metal which melts at 320.9°C. It is similar in many respects to Zn but forms more complex compounds. In Pearson’s classification, the large and easily polarized Cd cation is a soft Lewis acid, whereas, Zn is borderline. Cd\(^{+2}\) is thus likely to combine with easily oxidized and soft ligands in which sulphur containing one is important in biology. Therefore, Zn is expected to be displaced by Cd in many proteins and enzymes in which Zn has sulphur dominated coordination sphere.

**Sources of Cadmium**

Cd is excessively used in the manufacturing of plastics, solder alloys, nickel-Cd batteries, photo-cells etc. Contamination of animal
feeds may also occur from burning coal, smelters and application of sewage sludge and phosphate fertilizers produced from phosphatic rocks or usage of polluted ground water/mining and industrial effluents.

**Cadmium content in soil, feeds and water**

*Cd* enters soil from natural as well as anthropogenic sources. Only 10% of total Cd in the environment is derived from natural sources. In nature, Cd occurs in association with Zn and lead, contamination of soil and crops may occur from smelter plants of Zn, copper and lead. Environmental contamination is very important since, Cd is one of the most bio-accumulative metals. Cd added to soil tends to be taken up into the leafy portions of plants, but it may sometimes reach toxic concentrations in grains. Cd content of feeds may vary widely with the agricultural practices such as use of phosphate fertilizer, sewage sludge and manure application. EC report (2003) indicated that Cd content ranged from 0.01 to 0.03 mg/kg in cereals, leaf vegetables, roots and tubers respectively. Oilseeds contained higher amounts of Cd (0.05 to 0.22mg/kg) while vegetable oils and fats had very low amount (0.002 to 0.003mg/kg). Peanuts, mustard and tobacco are high risk crops as they have high Cd uptake. Maximum permissible limits of Cd are 50 and 5 ppb for livestock and human drinking water, respectively (EPA, 2004).

**Maximum tolerance levels of Cadmium**
The upper limit of Cd in drinking water for livestock is reported to be 0.05 mg/L (EPA, 2004). Indian (Prevention of food adulteration act; PFA) permissible limit for Cd in human food is 1.5mg/kg. Animal offals such as kidney and liver exhibit high Cd values up to 1000 ppb (ATSDR, 1997). EC report (2003) horse meat contain higher concentration of Cd (upto 0.27mg/kg) compared to fish, milk, egg (0.001to 0.01mg/kg). FAO/WHO (2000) reported the critical value of Cd in finished meat product (1µg/g), muscle meat (0.1µg/g), and liver, kidney (0.5µg/g) respectively. The WHO has set 1mg/kg upper limit for Cd in complete feeds for animals (IPCS, 1992). The permissible limit for Cd in the kidney has been reported as 1 ppm (FAO/WHO, 2000). As per the recommendation of FAO/WHO (2000), the daily intake of Cd in man should be limited to 1µg/kg body mass and the weekly intake must not exceed 400-500 µg of Cd.

**Absorption, Metabolism, Storage and Excretion of Cadmium**

Cd is more efficiently absorbed from the lungs than from the gastrointestinal tract (ATSDR, 1989). In general, the intestinal absorption is low: 0.3% in goat, 0.035-0.2% in lactating dairy cow and 5% in swine, while 2-6% of dietary Cd is absorbed in humans. After exposure to normal dietary concentrations of Cd (10-30 µg/day), about 50% of the body burden is found in kidney, about 15% in the liver, and about 20% in muscle (Kjellstrom, 1979). Lower concentrations are found in brain, bone, and fat. After absorption Cd is transported through blood by binding to red blood cells and albumin. Subsequently it goes to the liver, where incorporation into metallothionine occurs. Slow excretion of Cd results in extremely long biological half-times in animals, lasting from 200 days to 22 years (Friberg et al., 1985). It has been estimated that 0.01% of the body load was excreted daily to a large extent via urine (0.5-2.0 µg/L), bile and gastrointestinal tract, saliva and sweat. Animal studies showed that the faecal excretion was considerably higher (80-90 % of total ingested) than the urinary excretion in goats and cows. Cd exposure irrespective of the source increased the daily urinary output, although total urinary excretion observed in goats and cows was low 0.03-0.05 % of the administered dose after oral ingestion (Bersenyi, 2003). Increased urinary and decreased fecal excretion of Cd was observed at 1 and 10 ppm level of Cd supplementation (Singh, 2004).

**Cadmium residue in animal products**

Cd in the diet not only affects the performance of animals but also affects the quality of milk and meat which in turn may pose a threat to human health. Houpert et al. (1997) reported that Cd in milk averaged 2 to 4.9% of blood clearance in Cd exposed
ewes. Cd content averaged 0.049 ± 0.008, 0.078 ± 0.007, 0.032 ± 0.012 ppm and 0.031 ± 0.002, 0.105 ± 0.042, 0.035 ± 0.013 ppm in liver, kidney and goat tissues samples collected from two agro-climatic zone 1 and 2 of Haryana respectively, (Kaur et al., 2007a). It is reported (ATSDR, 1997) that meat and fish normally contained Cd in the range of 5 to 40 ppb, however, animal offal such as kidney and liver can exhibit extraordinarily high Cd values, up to 1,000 ppb, as these are the organs in animals where Cd concentrates. Data from EC report (2003) indicated that meat products, fish, milk and eggs contained low amounts of Cd (0.001 to 0.01 mg/kg), with the exception of horse meat (up to 0.27 mg/kg).

Biological half-life of Cadmium
The binding of Cd by metallothioneine and deposition in the kidney and other soft tissues apparently accounted for its very long half-life in the body for humans values of 10-38 years have been reported and in case of cattle liver and kidney this value was < 2 years and > 12 years respectively (Kostial, 1986).

Effect of Cadmium on Oxidative stress
Reactive oxygen species (ROS) are often implicated in Cd-induced deleterious health effects. There are direct evidence of the generation of free radicals in animals following acute Cd overload and indirect evidence of involvement of ROS in chronic Cd toxicity and carcinogenesis. Cd-generated superoxide anion, hydrogen peroxide, and hydroxyl radicals in vivo have been detected by the electron spin resonance spectra, which are often accompanied by activation of redox sensitive transcription factors (e.g., NF-κB, AP-1 and Nrf-2) and alteration of ROS related gene expression. Cd stimulates the formation of metallothioneineins and ROS, thus causing oxidative damage to erythrocytes and various tissues resulting in loss of membrane functions (Sarkar et al., 1998). Long-term exposure to Cd increases lipid peroxidation and causes inhibition of superoxide dismutase (SOD) activity indicating oxidative damage in liver, kidney and testes (Patra et al., 1999). The increase in lipid peroxidation due to Cd toxicity have been attributed to alterations in the antioxidant defense system which includes enzymes such as glutathione peroxidase (GPx), glutathione-S-transferase, SOD, and catalase (CAT), and non-enzymatic molecule like glutathione, which normally protect against free radical toxicity.

Cd is a potent cell poison and it affects the ubiquitin/ATPdependent proteolytic pathway. However, the cellular mechanisms involved in Cd toxicity are still not well understood, especially in neuronal cells. The Cd-induced increase in protein-mixed disulfides (Pr-SSGs) and ubiquitinated proteins (Ub) are not affected when more than 85% of intracellular glutathione is removed from the cells by the glutathione synthetase inhibitor l-buthionine-(S, R)-sulfoximine. However, the reducing agent dithiothreitol, which prevents build-up of Pr-SSGs in the cell also blocks the accumulation of Ub proteins induced by Cd. In addition, dithiothreitol blocks the effects of higher (50 µm) concentrations of Cd on cytotoxicity and on glutathione, Pr-SSGs, and Ub proteins. So, changes in the levels of intracellular Pr-SSGs and ubiquitin-protein conjugates in neuronal cells are the responses closely associated with the disruption of intracellular sulfhydryl homeostasis caused by Cd-mediated oxidative stress. The testis is the important target organ of Cd toxicity. Many studies indicate that Cd induces testicular damage in many species of animals including mice, hamsters, rabbits, guinea pigs and dogs (Hew et al., 1993; Xu and Jiang 1996). It has profound effect on sex organ weight, a primary indicator of possible alteration in androgen status (Biswas et al., 2001; Laskey and Phelps, 1991).

An interesting mechanism explaining the indirect role of Cd in free radical generation was presented some years ago (Price and Joshi, 1983). In this mechanism it was proposed that Cd can replace iron and copper in various cytoplasmic and membrane proteins (e.g. ferritin, apoferritin), thus increasing the amount of unbound free or chelated copper ions participating in oxidative stress via Fenton reactions (Casalino et al., 1997). These results support very recent findings by Watjen and Beyersmann (2004). Displacement of copper
and iron by Cd can explain the enhanced Cd-induced toxicity, because copper, displaced from its binding site, is able to catalyze breakdown of hydrogen peroxide via the Fenton reaction. Cd is unable to generate free radical directly but replaces the copper and iron in various cytoplasmic and membrane protein thus increasing the free iron and copper ions participating in oxidative stress.

Kamiyama et al. (1995) reported increase in GSH concentration in rats given 0.228 ppm Cd thrice a week for a period of 1 year. Similarly, Rana (1996) and Shaikh et al. (1999) also reported increased GSH levels in Cd exposed animals. Hussain et al. (1987) found inhibition in the SOD activity in liver and kidney tissues exposed to Cd either in vitro or in vivo. They also reported increased lipid peroxide value. Mateo et al. (1997) reported decreased concentration of catalase in erythrocytes exposed to 0.2 mM Cd. Results of a study in yeast Saccharomyces cerevisiae, Liu et al. (2005) reported increased MT synthesis, MDA and activities of SOD and catalase when these were exposed to CdCl₂ up to 500 µM concentration.

**Effect on immunity**

In recent years it has been found that heavy metals have an adverse effect on the immune system of the animals. Cd altered immune response of animals which varies considerably upon dose and species of animals. Cd toxicity causes immuno suppression in animals and leads to host susceptibility to several bacterial and viral infections (Manna, 1997). Haneef et al (1995) observed a decrease in antibody titre against chicken RBC in goats given Cd chloride for 42 days. Boroskova and Dvoroznakova (1997) observed decreased humoral immunity in guinea pigs supplemented with Cd. Cell mediated immune response (CMI) monitored by delayed hypersensitivity reaction to non-specific sensitizer 2, 4-dinitrochlorobenzene (DNCB) was decreased in rabbits inhaled with Cd for 90 days (Amaranath, 1999). Muneendra (2009) and Kaur et al. (2010) reported that Cd supplementation retarded the cell proliferation in all Cd supplemented groups i.e Cd (10⁻³M, 10⁻⁴M, 10⁻⁵M, 10⁻⁶M) under in vitro conditions.

**Effect of Cadmium on haematological parameters**

Liu-zhong et al. (1996) described chronic Cd intoxication (1mg/kg body weight daily as CdCl₂ solution) in sheep and reported microcytic hypochromic anaemia. In addition, RBC counts, hemoglobin and PCV values were significantly lower than those in control group. Hanafy and Solton (2007) reported a reduction in red blood cells count and haemoglobin content, WBC count showed an increase in numbers in Egyptian goats administered orally for 2 weeks. Amarath. (1997) observed progressive decrease in Hb and low PCV in Cd exposed group of rabbits compared to unexposed group. Cattle grazing near Cd contaminated areas and zinc processing plants showed anemia and subnormal hemoglobin and PCV values (Kessel et al., 1990).

**Effect of Cadmium on bio-chemical parameters**

Yanardag (2007) reported that administration of Cd @2 mg/kg/day as CdCl₂ intraperitoneally given to rats for eight days and revealed an increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT), liver GSH and lipid per oxidation (LPO) levels. The activity of AST enzymes was significantly increased at 10 ppm level of Cd supplementation (Singh, 2004). Liu et al. (1996) observed an increase in blood urea nitrogen (BUN) and total serum protein with decrease in albumin levels when sheep were fed with CdCl₂ @1mg/kg body wt. Manna (1997) observed increased level of total serum proteins, serum creatinine, ALT and AST in young growing calves fed with CdCl₂ for a period of 90 days. Liao et al. (1997) observed increased serum creatinine in rats fed with CdCl₂ in drinking water at the rate of 50, 150 or 200 mg\ liter of water for 90 days. Amarnath (1999) studied the effect of Cd inhalation in rabbits and reported increased serum AST and ALT activity. He also observed increase in blood
Cd concentration of rabbits from 15th day of Cd inhalation.

**Effects of Cadmium on endocrine glands**
No adverse effects were seen on parathyroid glands of female Wistar rats exposed to 8 mg Cd/kg body weight/day via drinking water for 90 days (Kawamura et al., 1978). Paire et al. (1993) reported that Cd inhibits the enzymes S/ D-1 in liver and also reduced which essential for activity of thyroid.

**Effect of Cadmium on Production performance**
Inappetance is a common sign of chronic Cd toxicity. Experimental chronic Cd toxicity was found to reduce feed intake in cattle, which may be due to hyperkeratosis of fore stomach epithelium and degeneration changes in other organs. Calves given Cd in their diet shows decreased feed intake and body weight gain (Manna, 1997). Amaranath (1999) observed reduced feed intake in rabbits exposed to Cd in the form of CdO2. Growth rate decreased progressively with increase in Cd intake. Administration of Cd up to 10 ppm for 12 weeks in the diet of crossbred calves of about 4 months age had no adverse effect on DMI, nutrient utilization, growth performance and feed conversion efficiency (Kaur et al., 2007b). Phillips et al. (2004) observed that there was no effect on DM intake and digestibility in sheep given 286 µg Cd /kg DM intake but water retention was increased. (Masaoka et al., 1994) conducted a long term experiment on Rhesus monkey and observed decreased growth in animals given Cd @ 0.4 mg/ kg body weight/day, but no effect on growth was seen in monkeys given lesser amount of dose (0.12 mg/kg body weight/day).

**Effects of Cadmium on health of animals**
Cd is a well-recognized environmental pollutant with numerous adverse health effects. It principally affects lung, liver, kidney, and testes following acute intoxication, and nephrotoxicity, immunotoxicity, osteotoxicity and tumors on prolong exposures. Numerous studies have shown that acute inhalation exposure to Cd can cause death in human and animals. Acute inhalation of Cd oxide fumes had also led to death in rats, mice, rabbits, guinea pigs, dogs, and monkeys, with the mortality rate apparently being directly proportional to the duration of exposure and the concentration of inhaled Cd (Klimisch, 1993).

**Interaction of Cadmium with other antioxidants**
One of symptoms associated with Cd intoxication is the development of anemia in the exposed individual, a result of the inhibitory effect of Cd on iron metabolism and absorption. Ascorbic acid does not have a direct effect on Cd, but the nutrient improve iron absorption in gastrointestinal tract. Singh, (2004) reported that copper retention was significantly reduced in Cd treated calves. The disturbance in copper metabolism is the reduced plasma ceruloplasmin concentration by Cd and these copper deficiencies eliminate by increasing dietary copper intake. The interaction between Cd and calcium was hardly recognized until the development of the chronic Cd syndrome, Itai-Itai disease, in Japan. The bone deformities have been attributed to Cd deposits in bone tissue that interfere with calcification and bone remodeling (Wang and Bhattacharya, 1993). Both Cd and Zn are members of the group II B metals. Cd has a higher affinity for metallothionein and in fact displaces Zn from cysteine binding site. Underwood (1977) documented that high levels of dietary Cd lead to decreased absorption and tissue levels of Zn and symptoms of chronic Cd toxicity are similar to those of Zn deficiency. Nemmiche et al. (2007) reported that Cd treated group (Cd 2mg CdCl2/kg body weight/day and alpha-tocopherol 100 mg/kg body weight) induces an oxidation of cellular lipids and proteins and that administration of alpha-tocopherol can reduce Cd-induced oxidative stress and improve the glutathione level together with other biochemical parameters in western rats. Karbownik et al., (2001) reported the protective role of melatonin (reduced lipid peroxidation), as an effective antioxidant and free radical scavenger, against Cd toxicity. Ulusu et al., (2003) also studied the
protective role of selenium against Cd-toxicity by increasing the activity of Cd induced inhibition of glutathione reductase in rabbit.

CONCLUSION
Both natural and anthropogenic sources are responsible for environmental contamination with the Cd. Cd is listed by the US Environmental Protection Agency as one of 126 priority pollutants. Due to its slower rate of excretion from the body it has long biological half-times in animals (200 days to 22 years). Cd induced oxidative stress mostly due to its adverse effect on cellular defense system and intracellular glutathione levels and also by enhancement of the lipid peroxidation. This heavy metal not only affects the growth performances of animals but also it affects the hemato-biochemical parameters and general immunity and thereby susceptibility to several bacterial and viral infections is increased. The adverse effect of Cd can be ameliorated by the administration of vitamin E, selenium and Zinc due to their antioxidant nature.

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