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CADMIUM INDUCED PATHOLOGICAL AND ECO-TOXICOLOGICAL EFFECTS IN ANIMALS

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ABSTRACT

Present review article describes cadmium induced pathological and ecotoxicological effects of cadmium in animals. This is highly toxic non-essential transition metal, causing serious global problem to human health, animals and environment. After entered into human blood and its subsequent distribution cadmium imposes multiple morbidities in human. In mammalian system cadmium is reported to cause toxicity to liver, central nervous system, and kidney in animals and humans. It disrupts endocrine functions in humans and generates carcinogenic effects in mammary glands and acts as a metalloestrogen and evokes breast cancer. Cadmium is one of the important environmental factors involved in lipid peroxidation, it disrupts gastric mucosal barrier and induce gastric ulcers. Cadmium shows inhibitory effects on the nerve fibres and reduces the response to sympathetic nerve stimulation by affecting presynaptic nerve terminals. Cadmium (Cd) induces bone pathologies; it severely affects bone formation and structure. Long term exposure of cadmium is very vulnerable to immune system. It stimulates the production of cytokines and IgE antibodies. High levels of cadmium have been reported in cow milk that is very harmful to consumers. Its high bio-accumulation is observed in marine gastropods, fishes, frogs and turtles. It potentially induces oxidative stress and largely affects respiratory system in aquatic and marine animals. Higher levels of cadmium are also reported in blood samples of industry workers and causing occupational health hazards. This article suggests safety measures for workers engaged in industries and methods of detoxification of cadmium.

KEYWORDS: Heavy metals, Cadmium, Agricultural and Industrial sources, Toxicity and Physiological effects.

INTRODUCTION

In present time heavy metal pollution is a serious worldwide problem. This is increasing due to urbanization and increase in anthropogenic activities. Metals constitute a fundamentally important part of the total human environment. These are non-biodegradable materials that exist in different parts of the food cycle such as fruits and vegetables as commonly consumed foods.[1] Heavy metals are highly toxic and generate carcinogenic effects in human and animals.[1] These are responsible for adversities of all types but most of them are related to oxidative stress mediated toxicity of heavy metals involves damage primarily to liver (hepatotoxicity), central nervous system (neurotoxicity), DNA (genotoxicity), and kidney (nephrotoxicity) in animals and humans.[1] Heavy metals are reported to impact signaling cascade and associated factors leading to apoptosis.

Due to anthropogenic activities cadmium is available in soil, water bodies and contaminates food chain. Street dust is also an important source of cadmium and we get exposure every day from soil, air, and water. Its toxicity is a potential risk factor for living environment. It generally exists as a divalent cation, complexed with other elements (e.g., $CdCl_2$). Commercially, Cd is used in television screens, lasers, batteries, paint pigments, cosmetics, and in galvanizing steel, as a barrier in nuclear fission.

Cadmium is one of the most common and highly toxic non-essential transition metal poses a serious global problem to human health and animals. Cadmium is naturally occurring in the environment in form of divalent cation as a pollutant that is derived from agricultural and industrial sources. It enters into food chain through eatables and drinking water. In human it is transported through inhalation and ingestion. It indirectly generate various free radicals.[2] Cadmium (Cd) is highly toxic metal and affect glial architecture in the lizard *Podarcis siculus* (Table 1).[3] Cadmium reaches to aquatic systems from agricultural and industrial sources and its toxicity severely harm animal species, including soil, aquatic, and marine invertebrates.[4]

Though, other heavy metals lead (Pb), chromium (Cr), cadmium (Cd), arsenic (As), copper (Cu), strontium (Sr) and thallio (Tl) are detected in agriculture fields with sewage water.[5] Heavy metals enter the human body through respiratory, cutaneous, and gastrointestinal pathways and then accumulate in different organs, leading to their encountering with various parts of the body (**Figure 1)**. Cd is also detected in milk, urine and blood from where it is transported to various target organs.[6] Cadmium from all these sources facilitates its interaction with the immune system and significantly increases risk of cancer (Table 1).[7]

Cadmium (Cd) is one of the most harmful metals, being toxic to most animal species, including soil, aquatic, and marine invertebrates.[8] It is absorbed inside the glandular and muscles and gills, it potentially induces oxidative stress and chokes respiratory system in aquatic fish fauna and smaller invertebrates[9][10] Its high bio-accumulation has been observed in marine gastropods, the periwinkle (*Littorina littorea*) in its midgut gland.[11] Human exposure to Cd occurs chiefly through inhalation or ingestion. But in dairy animals it is transported through drinking water, and finally secreted in milk that is too harmful to consumers of all ages.[12] It severely affect bone and neurodevelopment in neonates (Table 1).[13] Its exposure causes renal problems[14] Cadmium impairs sperm quality mainly sperm fertilizing capability in both humans and non human primates.[15] Cadmium imposes clinicopathological and biomedical implications in man and other animals(**Figure 1)**.[15] Cadmium is reported very harmful to industry workers, generates irreversible toxic effects and occupational health hazards.[16]

Cadmium induced morbidities

Long term cadmium exposure leads to damage of liver, CNS and target renal system.[17] Cd causes kidney injury, homeostasis, bone mineralization and fertilization. It's exposure decreases glomerular filtration rate in nephrons and generates chronic kidney disease.[14] Cd exposure imposes multiple organ toxic effects in fetuses during pregnancy. It enters through placenta and causes teratogenicity, severely affects central nervous system, liver and kidney in fetuses.[18] Cadmium disrupts blood-testis barrier (BTB) via specific signal transduction pathways and signaling molecules, such as p38 mitogen-activated protein kinase (MAPK).[19] Cadmium imposes chronic neuronal dysfunction and neurodevelopmental disorders.[20] Cadmium acts as oxidative stress inducer.[21] Long term cadmium exposure starts breast cancer progression. Its acute expsoure promotes estrogen receptor-mediated gene expression that results in increased cell growth, migration and invasion. A chronic cadmium exposure stimulates the expression of SDF-1 by altering the molecular interactions between ERα, c-jun and c-fos.[22]

It is responsible for health problems in children as allergy, disorders in the endocrine system, and even neurodevelopment delay and disorder.[13] Exposure of sub-lethal concentrations of heavy metals affects growth and reproduction in *D. magna* a cladoceran.[22] Cd-responsive genes can be used as candidate biomarkers for monitoring aquatic pollution by heavy metal (**Figure 1)**.[8]

Cadmium as a strong carcinogen

Breast cancer development has been linked to the powerful environmental pollutant cadmium.[23] Due to their increased risk of breast cancer, cadmium metal complexes have been discovered to be extremely carcinogenic.[7] By acting as metalloestrogens—metals that bind to estrogen receptors and mimic the effects of estrogen—cadmium contributes to the growth of breast cancer.[24] In prenatal exposure to the metalloestrogen cadmium affects mammary gland development in human females before having an impact on the start of puberty. The neonatal mammary gland experiences an increase in mammosphere-forming cells, while the prepubertal mammary gland experiences an increase in branching, epithelial cells, and density as a result of its exposure. Exposure to cadmium increases estrogen receptor-alpha expression, which may raise the risk of breast cancer (Figure 1).[25]

Effect of cadmium on aquatic life

Cadmium is an extremely hazardous metal and industrial activities are making it more prevalent in the environment. A harmful heavy metal called cadmium (Cd) may cause oxidative stress in young *T. obscurus* fish. The hazardous contaminant cadmium (Cd) has a negative impact on *Sinopotamon henanense*, a freshwater crab that lives in benthic region.[8] Cd builds up inside crab muscles and interferes with the activity of crucial genes, perhaps resulting in candidate biomarkers for heavy metal pollution monitoring in aquatic environments.[8] The periwinkle (*Littorina littorea*), a marine gastropod, is adversely affected by cadmium (Cd). It causes significant cytological and tissue-specific changes and builds up in high concentrations inside the crab midgut gland. Pathological cellular disturbances are caused by reversible damages caused by cadmium exposure.[11] *Mytilus galloprovincialis'* digestive gland is impacted by cadmium exposure, which also induces lysosomal acidification.[26] Dam water has been shown to have high levels of cadmium, which significantly damages aquatic animal life (Figure 1). It results in bone mineralization, renal damage and changes in the homeostasis of vital elements. It enters the foetus through the placental membranes and causes teratogenicity in the liver, kidney, central nervous system, and other organs.[18] *S. rhombeus* is significantly harmed by Cd, which is a potential ecological risk factor (Table 1).[10]

Effects of Cd exposure in terrestrial animals

Cadmium is a highly toxic metal and its levels in the environment are increasing due to industrial activities. Spiders *Pardosa pseudoannulata* is one of the most common wandering

spiders in found agricultural fields and a potentially good bio-indicator for heavy metal contamination. Cadmium passes through the blood-brain barrier and causes neurotoxic activity. An acute exposure of cadmium disturbs the glial architecture in the lizard *Podarcis siculus*, and acts at cellular and molecular levels.[3] Cd causes toxicity in rat gastric fundus.[2] It significantly damages pathways in lysosomes and phagosomes.[27] Cd also causes oxidative stress through essential ions, apoptosis, interference with selected signaling pathways and epigenetic regulation of genes (Table 1).

Effect of cadmium on endocrine function

Environmental toxin cadmium (Cd) is a potent disruptor of human endocrine functions. It interferes with ovarian function and the hypothalamus-pituitary-gonadal axis.[28] It builds up by bio-magnification and settles inside the kidney, liver, and gills. It causes toxicity in males and structural damage to the blood-testis barrier and testis vasculature. Leydig cells, seminiferous tubules, and blood arteries in the testis are all affected by cadmium. Cd results in tissue inflammation and the formation of necrotic regions. By causing structural alterations and apoptotic cell death it adversely impacts germ cell development at all stages. Damage to the Sertoli cells leads to cytoplasmic rearrangement and disruption of the inter-Sertoli tight junctions, which increases the blood-testis barrier's permeability. Consequently, major structural alterations in the Leydig cells significantly decreased the testosterone secretion. Testis Cd poisoning severely lowers sperm count and testis functions in both humans and other animals.[29] Seminiferous tubule atrophy is followed by interstitial revascularization and Leydig cell renewal.[29] Reports on cadmium-induced testicular oxidative stress and apoptosis in rats are also available. In (Figure 1)[30] Vascular endothelial cells and smooth muscle cells undergo a variety of morphological and physiological alterations after prolonged Cd exposure to blood arteries (Table 1).

Cadmium (Cd^{2+}) exerts significant effects on ovarian and reproductive tract morphology. Its presence is also observed in placenta in pregnant females where it decreases birth weights and force premature birth. Cadmium also shows stimulatory effects of on ovarian progesterone synthesis, due to enhanced conversion of cholesterol to pregnenolone by the cytochrome P450 side chain cleavage (P450scc).[31] At low dosage it stimulates ovarian luteal progesterone biosynthesis and high dosage inhibiting it. Cadmium may have diverse physiological functions in both exocrine and endocrine pancreatic cells.[32] It severely affects exocrine pancreatic secretion and plasma levels of pancreatic polypeptide (PP). Exposure to

cadmium led to a decrease in PTH levels, while exposure to lead increased PTH levels (**Figure 1)**. It also affect function of calciotropic hormones, parathyroid hormone (PTH) and calcitonin which are involved in the regulation of bone mineral metabolism and maintenance of calcium and phosphate homeostasis in the body(Table 1).[33]

Effects on spermatogenesis

Cadmium is known to exert toxic effects on multiple organs, including the testes. Its exposure severely affects spermatogenesis in dose dependent manner.[34] It impairs sperm quality mainly sperm fertilizing capability in both humans and in non human primates.[15] Cadmium affects the production and secretion of sex steroids and reduce rate of gametogenesis in *R. decussates* (**Figure 1)**.[35] It severely affects secretion of sex hormones mainly FSH level in postmenopausal women(Table 1).[36] It causes reduction in distribution of the germ cell population.

Cadmium-induced impairment of the gastric mucosal barrier

Cadmium is one of the important environmental factors that disrupt gastric mucosal protection. Its exposure increased the rate of lipid peroxidation, and significantly reduced the mucin content ($P < 0.01$) and prostaglandin levels ($P < 0.05$) of mucosa in treated experimental animals. This is highly vulnerable to gastric mucosal functions and responsible for the high incidence of stress-induced gastric ulcer in the population **(Table 1)**.[37]

Effect of cadmium on nerve function

Cadmium shows neurotoxicity and shows inhibitory effects on the sciatic nerve fibres.[38] Cadmium ($CdCl_2$) reduces the response to sympathetic nerve stimulation primarily through an effect on presynaptic nerve terminals.[39] $CdCl_2$ (1 mM) shows inhibitory effects on taste nerve responses in mice.[40] It also affects calcium function at presynaptic nerve terminals[41] and causes cytotoxicity in multiple organs including the brain.

Effect of cadmium on bone function:

The skeleton suffers damage from low-level chronic exposure to cadmium (Cd). It has a sizable negative impact on bone microstructure, bone biomechanical properties and bone mineral density.[42,43] Cadmium (Cd) cause disease in the bone and has a negative impact on bone growth, structure, and characteristics.[44] Cd impacts bone structure and function more in women than in men.[45] Skeletal demineralization resulted from exposure to cadmium, which may interact directly with bone cells, reduce mineralization and also block the

formation of collagen and procollagen C-proteinases.[46] It manifests as the Itai-Itai illness. In post-menopausal women, it raises the risk of osteoporotic fractures, which can lead to disability. Along with osteomalacia, this also indicates extensive bone decalcification.[47] Lower serum PTH levels brought on by increased cadmium exposure could cause the release of calcium from bone tissue.[48] Cadmium also affect calcium metabolism and absorption of vitamin D_3 and action on collagen fibers. Severe cadmium poisoning imposes osteomalacia or osteoporosis.[46] Zinc supplementation in rats shows protective effects on bone metabolism in male rats chronically exposed to cadmium.[45]

Renal damage in cadmium toxicity:

Renal impairment has reportedly been caused by prolonged occupational and environmental exposure to cadmium.[49] In addition to other tissues including bone and the placenta, cadmium primarily accumulates inside the kidney and liver. Early symptoms of renal injury, proteinuria, calcium loss and tubular lesion are displayed by cadmium exposure.[50] It has an impact on reserve filtration capacity and glomerular filtration rate (GFR). Additionally, it results in nephrotoxicity, which has side effects include impaired buffering capacity, polyuria, hyperphosphaturia, hypercalciuria, glucosuria, and aminoaciduria.[51] There was a loss of calcium, amino acids, enzymes, and an increase in proteins in the urine as a result of the significant cellular damage and functional integrity in the proximal tubules. Beta 2-microglobulin, retinol-binding protein, and alpha 1-microglobulin are the most often found proteins in urine.[52] Long-term exposure to cadmium is harmful to people's health in many ways.

Effect of cadmium on immune function:

In addition to causing organ and tissue damage, Cd also functions as an immunotoxic agent by controlling immune cell activation and death. It drastically modifies immune cytokine output, resulting in the generation of reactive oxygen species (ROS) and oxidative stress. It modifies the synthesis of specific antibodies in immune cells and the frequency of T lymphocyte subsets.[53] At relatively low cadmium levels, the body's presence of the metal has immunosuppressive effects (Table 1).[54] Circulating B and T lymphocytes, NK cells, and immune memory cells are all impacted by Cd. The cytokine and IgE antibody production is stimulated by cadmium.[55] Immune systems are extremely sensitive to long-term cadmium exposure. CdCl2 inhibits the production of RNA and DNA in B-cells and has immunotoxic effects on humoral immunity. CdCl2 also imposes inhibitory effects on B-cell activation and

the production of specific Ig isotypes. It influence the ability of B-cells to mount effective immune responses to pathogens (Table 1).[56]

Detoxification:

The overall environment of humans is fundamentally important in terms of metals. Since complex mixures of metal compounds and presumably chemical molecules that may be carcinogenic in and of themselves are frequently present in human exposure, interactions between these compounds may dramatically increase the risk of cancer in humans.[7] The primary pathways of cadmium carcinogenesis may be related to oxidative stress induction, inhibition of apoptosis, DNA damage repair inhibition and gene expression suppression. Cadmium may also exert its effects through abnormal DNA methylation. Numerous biological functions, including signal transduction pathways, cell proliferation, differentiation and apoptosis are impacted by cadmium. Epigenetic effects of cadmium have been described as the down-regulation of methyltransferase enzymes and a reduction in DNA methylation. Additionally, raising the concentrations of intracellular free calcium ions triggers neuronal death in addition to other deleterious influence on the stability of the genome.[57]

A powerful carcinogen, inducer of antioxidant enzymes, and complexer of glutathione (GSH) and metallothionein (MT), cadmium (Cd) is a non-essential transition metal. The most effective defences against Cd-induced oxidative damage are these enzymes. Additionally, defence mechanisms include chaperone expression, mitophagy inhibition, ER stress prevention and metabolic stress prevention.[58] In addition, *Littorina littorea* expresses a Cd-specific metallothionein (MT), which is expected to perform a protective role against the unfavourable intracellular effects of this metal given its molecular characteristics.

Cadmium toxicity can be reduced by partial hepatectomy, which caused a significant reduction in the rate of DNA biosynthesis. It also inhibited the regenerative process of the liver, probably by inhibiting thymidine kinase.[59] Both magnesium and selenium had a protective effect against cadmium toxicity in the isolated perfused rat liver system.[60] Certain chelating agents such as DMSA and MiADMSA and calcium trisodium diethylenetriaminepentacetate (CaDTPA) reduce the toxicity of cadmium. These two substances reduce the concentration and toxic effects of cadmium in the body.[61] EDTA significantly increased urinary cadmium excretion. Dimercaprole [British anti-Lewisite (BAL)] is an effective antidote for heavy metal poisoning.

Cadmium affects gene transcription in the liver of the freshwater turtle (*Chinemys reevesii*).[62] Cd promoted MT mRNA transcription in turtle liver at low dose (7.5 mg/kg) and inhibited MT mRNA transcription in turtle liver at medium dose (15 mg/kg) and high dose (30 mg/kg). Cd inhibited mRNA transcription of SOD, CAT, and PNKP in turtle liver, and the inhibition was evident at a high dose (30 mg/kg). Cd promoted GPX4 mRNA transcription in turtle liver, especially at low dose (7.5 mg/kg).

Natural antioxidants are useful in neutralizing the effects of cadmium. Vitamin E, vitamin C readily reversed cadmium toxicity in male rats. Cadmium extracts of moringa, graviola, ginger, and artemisinin are used in combination with a potent chemopreventive and chemotherapeutic agent to provide antioxidant protection against DMBA-induced breast cancer tumors resulting from cadmium toxicity.[63] Nitric oxide synthase (T-NOS) and malondialdehyde (MDA) levels were significantly increased (P-andlt; 0.05).[64]

Vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol) are good antioxidants and have protective effects against cadmium-induced toxicity in various experimental animals.[65] Vitamin A, C, E and selenium can actually prevent or reduce many toxic and effects. Effects of cadmium on certain organs and tissues such as the liver, kidneys, bones and blood. As a result, lipid peroxidation increased and glutathione levels decreased in the intestine of rats. This combination showed a protective effect of the combination against cadmium toxicity in the intestine.[2] Other elements include zinc and magnesium, which have many clinical applications. Zinc has been suggested to strengthen the immune system and prevent the formation of free radicals. Magnesium is an important co-factor in the activation of many human enzyme systems. Zn and Mg can reverse Cd-induced nephrotoxicity. Cadmium toxicity reduces the content of antioxidant enzymes, generates reactive oxygen species and lipid peroxidation. In fact, Zn and Mg can neutralize reactive oxygen species and lipid peroxidation.[66]

Application of nanoparticle in the treatment of cadmium poisoning:

Al2O3 nanoparticles can absorb cadmium. In general, Al2O3 nanoparticles are suitable for the removal of Zn and Cd from solution/sorbent systems. Al2O3 nanoparticles with low citrate content are used to remove Cd and Zn from contaminated solutions.[67] Carbon nanotubes (CNTs) remove metal ions from aqueous solutions.[68] Cadmium can be removed from wastewater with nano-sized TiO2 particles.[69] Salinity acted as a protective factor that could reduce levels of reactive oxygen species and malondialdehyde. In addition, salinity can

strengthen the antioxidant defense system, including superoxide dismutase, catalase and glutathione. Na/K-ATPase activity was significantly reduced in gills, kidneys, and intestines upon Cd exposure.[8]

Plasma exchange can reduce heavy metal toxicity.[70] It is offered in emergency situations. removal of cadmium is also possible by dialysis. In severe renal impairment, hemodialysis is useful to replace kidney function.[71] Some toxic substances can be strongly bound to plasma proteins and cannot be removed by hemodialysis. Plasmapheresis is practical and acceptable for removing protein-bound heavy metals from plasma. However, there are no controlled trials of plasmapheresis for any specific toxicity.[72] *Littorina littorea* expresses a Cd-specific metallothionein (MT), which, due to its molecular properties, is expected to protect against the harmful intracellular effects of this metal.[11]

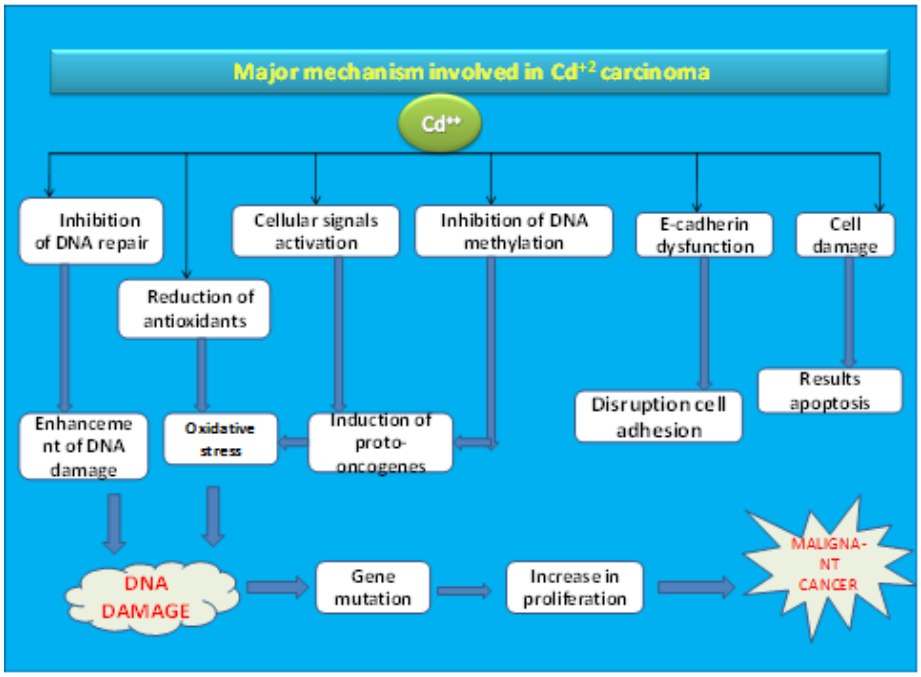

Figure 1: Showing major mechanism involved in cadmium induced carcinoma.

Table 1: Showing various heavy metal induced toxicity in animals with special reference to vertebrates.

S.N	Heavy metal compound/s	Biological effects in organ systems	References
1	Experimental Cd(2+) exposure	Cd in rat gastric fundus	[2]
2	cadmium (Cd)	Damage of glial cells functions morphological cellular alterations in the brain in lizard Podarcis siculus	[3]

3	cadmium (Cd)	Environmental and trophic chain contamination	[5]
4	Cd exposure	Gills' damage in fishes	[10]
5	Cadmium divalent Cd(II)	*Littorina littorea* expresses a Cd-specific metallothionein	[11]
6	Cadmium sulfate and chloride	Inductors of stress and modulator of different factors such as: protein kinase and phosphatase, caspases, mitochondria, heat shock proteins, metallothioneins, transcription factors, Reactive oxygen species.	[11]
7	Cadmium divalent Cd(II), Cadmium high levels	Detected in cow milk that is very harmful to consumers of all ages	[12]
8	Cadmium sulfate and chloride	Impair sperm quality in non human primates	[15]
9	Cd exposure.	Impose multiple organ toxic effects in fetuses after the exposure to Cd during pregnancy	[18]
10	Cadmium divalent Cd(II), Cadmium high levels	Decrease fertility in men due to alteration in testis function and reduction in sperm count;	[19] [23]
11	Cd exposure.	oxidative damage	[27]
12	cadmium (Cd)	Cd-induced toxicity evoke breast cancer progression	[23]
13	cadmium (Cd)	Cadmium increases stem/progenitor cells, cell density, and expression of estrogen receptor-alpha in breast cancer patients	[25]
14	environmental Cd(2+) exposure	Structural damage to testis vasculature and blood-testis barrier, inflammation, including cytotoxicity on Sertoli and Leydig cells	[28]
15	environmental Cd(2+) exposure	In blood vessels Cd exposure causes various morphological and physiological changes in vascular endothelial cells and smooth muscle cells	[28]
16	environmental Cd(2+) exposure	Spermatogenic cells underwent irreversible degeneration or atrophy of seminiferous tubules in birds	[29]
17	environmental Cd(2+) exposure	Activities of superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, and testosterone were also increased.	[29]
18	environmental Cd(2+) exposure	Cd(2+) may affect steroidogenesis, inhibit the actions of endogenous estrogens	[31]
19	Experimental Cd(2+) exposure	Avert physiological functions in both exocrine and endocrine pancreatic cells	[32]

20	Experimental Cd(2+) exposure	Dysfunction of energy status and the endocrine disruption which could impede reproduction.	[35]
21	Experimental Cd(2+) exposure	Generate reactive oxygen species (ROS)	[38]
22	Experimental Cd(2+) exposure	Effects of cadmium and lead on adrenergic neuromuscular transmission in the rabbit	[40]
23	Experimental Cd(2+) exposure	Effect of cadmium on the isolated phrenic nerve-diaphragm is largely due to inhibition of calcium function at presynaptic nerve terminals.	[41]
24	Experimental Cd(2+) exposure	Changes in the serum concentration of calciotropic hormones and disorders in Ca and phosphate metabolism	[42]
25	Experimental Cd(2+) exposure	Inhibitory effect on HA nucleation and growth, bone mineral dissolution	[44]
26	Cd exposure	Inhibition of Na+/K+–ATPase activity in gill, kidney and intestine	[53]
27	Experimental Cd(2+) exposure	Acts as an immunotoxic agent by regulating the activity and apoptosis of immune cells, altering the secretion of immune cytokines, inducing reactive oxygen species (ROS)	[53]
28	Experimental Cd(2+) exposure	Effects of cadmium associated with the humoral immune response are not due to an impairment of lymphocyte proliferation, an intermediate step involved in the generation of an immune response**,** the immunosuppressive effects	[54]
29	Experimental Cd(2+) exposure	Cadmium stimulate the production of cytokines and IgE antibodies, diminished number of B and T lymphocytes, and a considerable decrease in the number of NK cells.	[54]
30	Experimental Cd(2+) exposure	Selective effects on the production of specific Ig isotypes	[56]
31	Experimental Cd(2+) exposure	Cadmium affects multiple cellular processes, including signal transduction pathways, cell proliferation, differentiation, and apoptosis. Down-regulation of methyltransferases enzymes and reduction of DNA methylation	[57]
32	Experimental Cd(2+) exposure	Hepatectomy, caused a marked decrease of the rate of DNA biosynthesis	[59]
33	cadmium (Cd)	Cd-induced oxidative stress.an	[58]

		increased risk of carcinogenesis	
34	cadmium (Cd)	Reactive oxygen and nitrogen species, an increased risk of carcinogene	[58]
35	Experimental Cd(2+) exposure	Induce gene transcription of liver in freshwater turtle *Chinemys reevesii* exposed to cadmium (Cd	[62]
36	cadmium (Cd)	Impairs laying performance, egg quality, and eggshell deposition and induces oxidative stress and inflammation in the eggshell glands of laying hens	[64]
37	Cadmium divalent Cd(II)	Mammary gland tumors	[63]
38	environmental Cd(2+) exposure	Bioaccumulation in all target organs the liver, kidney, testes	[73]
39	Experimental Cd(2+) exposure	Affect iron metabolism by increased uptake of transferrin	[74]
40	Experimental Cd(2+) exposure	Detrimental effects on cadmium spermatogenesis	[74]
41	Cadmium divalent Cd(II)	Pathological cellular disruptions, apoptosis and autophagy	[75]
42	Cd exposure.	Lysosomal acidification of *Mytilus galloprovincialis*	[76]

CONCLUSION

Cd is a very toxic heavy metal in the environment; it causes multisystem toxicity in humans and other animals. It enters the body through ingestion and inhalation and disrupts the body's neuroendocrine, kidney, stomach, respiratory and reproductive functions. It also adds to food as a contaminant. It causes severe long-term physiological and biochemical changes in humans and animals upon exposure. Its existence can be limited by conscious programs for ordinary people. In nature, cadmium occurs as a pollutant and is transferred to different parts of the human body through inhalation of contaminated food, water and the environment. It affects the immune system, which is known to play a central role in the pathophysiology of cancer. Cadmium (Cd) is one of the most harmful metals for freshwater and marine invertebrates. These sources and natural properties of heavy metals facilitate their interaction with the immune system. New, advanced engineering methods and equipment can help reduce cadmium levels and remove them from the bodies of exposed people. Its detoxification is also possible with the help of chelators and solvents. However, chelating agents for cadmium poisoning are readily available, safe and effective without aggravating the host organ.

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