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Review Article

Heavy Metal Toxicity (Cd and As), their Possible Source of Contamination in Food Chain, Toxicokinetic and Ameliorative Measures; A Review

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Abstract

Heavy metals by their definition can be defined as those metals having an atomic number greater than 20 and an atomic density more than 5 g cm^{-3} and must exhibit the properties of metal. Heavy metal contamination of feeds and fodder imposes a great problem for livestock health, which is transmitted to the human body through the food chain by accumulating in milk, meat and egg products. Both natural (volcanic eruptions, forest fires) and anthropogenic (mining, burning of fossil fuels, automobiles exhaust, tobacco smoke) sources are responsible for the emission of arsenic into the atmosphere. The atmospheric arsenic will reach the earth's surface through air currents and rainfall which gets accumulated in the soil. The soil concentration of arsenic and cadmium ranges from 0.2 to 40 ppm and 0.1 to 0.5 ppm respectively [19]. Cultivation of fodder crops by excess application of fertilizers (Eg: phosphorus major source of Cd), pesticides (arsenal fungicides) act as a secondary source for contamination of animal feedstuffs and ingredients.

Through the contaminated feedstuffs, water and polluted air heavy metals can enter into the animal body systems resulting in severe health hazards in livestock species. Chronic exposure of livestock to heavy metal pollutants causes mutagenicity, carcinogenicity, teratogenicity, immunosuppression, poor body condition and impaired reproduction.

Keywords: Heavy Metal; Arsenic; Food Chain; Cadmium; Teratogen; Mutagen

Introduction

Metals are ubiquitous and prevail all over the earth including terrestrial ecosystem, atmosphere, hydrosphere and can enter and accumulate in biological organisms like plants and animals by the process of biomagnification. Heavy metals by their definition can be defined as those metals having an atomic number greater than 20 and an atomic density more than 5 g cm^{-3} and must exhibit the properties of metal [18]. Heavy metals were categorized under the group of environmental pollutants due to their adverse effect on the ecosystem and living organisms. There are certain metals viz., Cobalt, Chromium, Copper, Iron, Molybdenum, Magnesium, Nickel, Selenium and Zinc having a functional role and considered as essential nutrients for the proper functioning of plants and animals, results in deficiency diseases if they are not provided in adequate quantities and causes toxicity if supplied above the required quantity. Meanwhile, certain heavy metals result in acute or chronic toxicities even at very low concentrations (Arsenic and Cadmium).

In general, soil acts as a major sink for various heavy metals through sorption onto the metal oxides like ferromagnesian oxides, clay minerals, soil organic matter and humic substances [2]. The concentration of heavy metals in soil mainly depends on the parent material from which the soil is formed. The accumulation of heavy

metals in agricultural soils for a long period reduces the soil beneficial microbial population significantly and imposes a greater risk to the health of humans and animals [12]. However, the heavy metal uptake and bioaccumulation are directly controlled by soil cation exchange capacity, which in turn depends on several indirect factors such as soil pH, salinity, and metal concentration. Fodder crops are grown on the excess application of chemical fertilizers (P fertilizer source for cadmium), pesticides (organo-chemicals source for arsenic), and weed killers which can act as a major source of heavy metal accumulation leading to toxicity in animals. Arsenic and Cadmium are the potential accumulative toxins in the dairy production system.

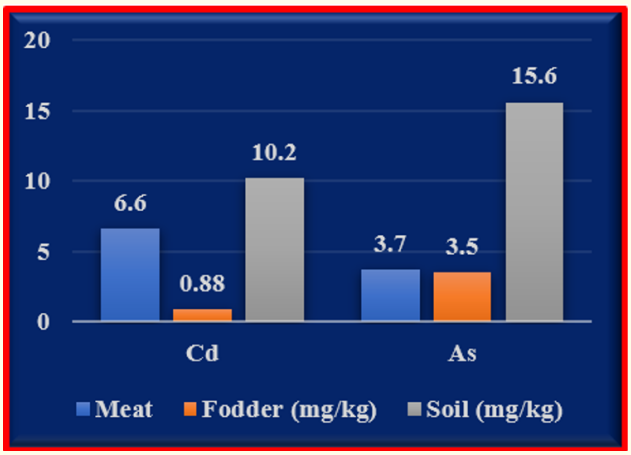

Figure 1: Cadmium and Arsenic concentration in different samples [25].

Chronic exposure of livestock to heavy metal pollutants causes mutagenicity, carcinogenicity, teratogenicity, immunosuppression, poor body condition and impaired reproduction. Especially in case of reproductive system the effect of toxicity is shown in two ways i.e., reproductive toxicity which deals with the target of metals on gonads and Developmental toxicity which shows effect on metal on fertilized ovum, embryo's, fetus and offspring [35].

This paper is mainly focused on the heavy metal toxicity of Arsenic and Cadmium in feeds and fodder and their source of contamination, mode of entry, mechanism of action and their effects on livestock.

Metal	Livestock's drinking water (µg/ml)	Irrigation water (µg/ml)	Soil (µg/ml)	Fodder crops (µg/ml)
As	0.20	0.01	20	0.10
Cd	0.05	0.01	3.0	0.10

Table 1: Maximum permissible limits of As and Cd in different samples [1].

Heavy metal toxicity: arsenic

From in public point of view, the word arsenic is synonymous with the word "poison" [11]. It is a metalloid, the 20th most abundant element on earth and occupies the 33rd position in the periodic table. Arsenic exists in two forms viz., inorganic and organic along with different oxidation states like trivalent and pentavalent. The organo-arsenical contamination in feedstuffs is the major source of poisoning in livestock, due to the adoption of faulty farming activities like indiscriminate use of chemical fertilizers and pesticides (insecticides, fungicides and herbicides). Arsenic intoxication in livestock mainly occurs in an acute or per acute and chronic form.

Sources of arsenic toxicity

Arsenic is generally found in an environment like soil, groundwater and plants. The report [24] revealed that the average concentration of Arsenic in a rural and urban environment is about 1 to 3 ng/m^3 and 20 to 30 ng/m^3 respectively. Both natural (volcanic eruptions, forest fires) and anthropogenic (mining, burning of fossil fuels, automobiles exhaust, tobacco smoke) sources are responsible for the emission of arsenic into the atmosphere. The atmospheric arsenic will reach the earth's surface through air currents and rainfall which gets accumulated in the soil. The soil concentration of arsenic ranges from 0.2 to 40 ppm with an average of about 5 to 6 ppm [19]. It is estimated that about 80 per cent of the total amount of arsenic released by anthropogenic activities into the atmosphere resides in the soil and gets accumulated in the various vegetative parts of the crops grown on these arsenic-contaminated soils [34]. Indiscriminate use of chemical fertilizers (source for As and Cd Table 3) and pesticides act as a secondary source of contamination of animal feedstuff. The use of polluted groundwater also serves as one of the major sources of arsenic poisoning in livestock. The dipping and spraying of arsenic-containing

fluids on livestock to control the ectoparasites are common sources of arsenic poisoning.

Food material	As content (ppm-dry weight)
Milk	0.0005-0.07
Eggs	0.005
Chicken	0.02
Crab	27.0-52.5
Crawfish	12.0-54.5
Shrimp	1.28-41.6
Pork	0.22-0.32
Tuna	0.71-4.6

Table 2: Arsenic concentration of different feedstuffs [6].

Fertilizer	As (ppm)[1]	Cd (ppm)[2]
NPK	1.67	-
Zinc sulphate	0.34	-
Super Phosphate	0.38	37.46
Urea	0.27	8.5
Di-ammonium phosphate	0.79	34.2
Mono ammonium phosphate	0.40	32.4

Table 3: Arsenic content of commonly used chemical fertilizers [6,29].

Mode of entry

In the animal body, arsenic enters through animal feed, green fodder, drinking water pharmaceutical medicines, secondary sources are accidental exposure to the limed fields, mineral supplements having a large content of trace metals and licking of painted surfaces containing metallic pigments.

Ingredients	As content (ppm)
Cottonseed cake	0-0.65
Mustard oil cake	0.33-0.64
Concentrated mixture	0.34-0.53
Pellets	0.27-0.57
Wheat bran	0.35-0.45
Grains	0.32-0.63
Mineral mixture	0.33-0.61

Table 4: As the content of concentrated feeds, [6,31].

Toxicokinetic of Arsenicals

Absorption and transport

Arsenic as a toxicant exerts its biological function when gets accumulated in cells and tissues [13]. Trivalent arsenic is a more toxic and highly soluble form that can easily be absorbed orally. Aquaglyceroprotiens (AQPs) are membrane proteins that play an important role in the uptake and transport of arsenic into the cells. Several studies revealed that the AQPs significantly get expressed in several organs such as liver, lungs, kidney, spleen, adipose tissue and the decreasing order of arsenic concentration in different tissues: kidneys > lungs > urinary bladder > skin > blood > liver [17].

Mechanism of arsenic toxicity

The mechanism of arsenic toxicity differs with the type of compound (pentavalent and trivalent).

Trivalent arsenic toxicity

Trivalent arsenicals readily react with thiol group molecules such as Glutathione and cysteine [26]. The binding of these arsenicals to the thiol group may result in inhibition of several biochemical activities which could lead to arsenic toxicity. Normally Pyruvate dehydrogenase oxides pyruvate to acetyl CO-A, a precursor to intermediates of the citric acid cycle which yields ATP as a source of energy for various metabolic activities of animals. The trivalent form of arsenic may bind to the lipoic acid (dithiol) moiety of the Pyruvate dehydrogenase (PDH) and inhibits its activity [23] which ultimately results in reduced ATP production. A study [27] in arsenic administered rats resulted in depletion of carbohydrate levels in the body. Methylated trivalent arsenicals like MMA^{III} may alter the redox potential status of cells and lead to cytotoxicity by inhibiting glutathione reductase and thioredoxin reductase enzymes activity by binding at the thiol group position of these enzymes [28,16].

Pentavalent arsenic toxicity

Arsenate has a similar structure and properties to phosphate and can replace phosphorous in several biochemical reactions [8]. For example, Arsenate can inhibit hexokinase enzyme by the production of glucose-6- arsenate and 6-arsenogluonate when reacted with glucose and gluconate respectively as it replaces phosphate position and results in reduced ATP production by a process termed arsenolysis [8]. Whereas at the mitochondrial level, amino lysis may take place during oxidative phosphorylation by

the production of adenosine-5-diphosphate-arsenate in the sub-mitochondrial region by the reaction of ADP with arsenate in the presence of succinate. A study [7] observed a reduction of ATP production in the rabbits when exposed to arsenate (0.8Mm) under the *in-vitro* condition.

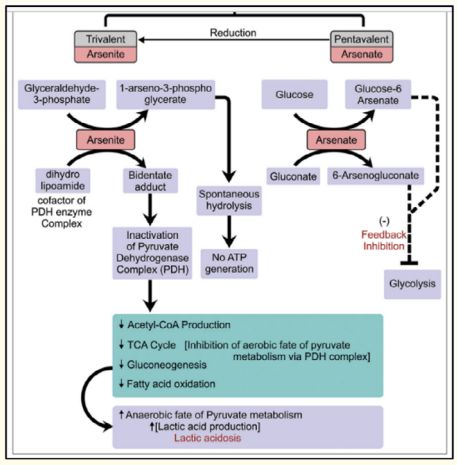

Figure 2: Schematic view of the mechanism of As^{III} and As^{V} [8].

Clinical manifestation of arsenical toxicity

Clinical findings of arsenic poisoning in animals are broadly classified as acute and chronic.

Acute poisoning

The clinical findings of acute arsenic toxicity are found all over the body systems. The most prominent sign of acute arsenic toxicity includes vomiting, nausea, profuse watery diarrhoea, severe abdominal pain and excessive salivation. Other symptoms include a diffuse skin rash, seizures and toxic cardiomyopathy, haematological abnormalities, renal failure, respiratory failure and pulmonary oedema. Various neurological problems include.

Encephalopathy or peripheral neuropathy. Recent poising of arsenic in the animal body can be indicated by the urinary arsenic concentration.

Chronic poisoning

In the case of chronic poisoning, arsenic gets accumulated in various tissues such as the liver, heart, kidneys, lungs, gastrointestinal tract, spleen and nervous system. It also gets accumulated in the keratin-rich tissues such as nails, skin and hair. The most prominent effect of chronic poisoning is a malignant change in every part of the body, increased risk of cardiovascular, respiratory, peripheral vascular disorders, diabetes mellitus and neutropenia. Dermatological changes include hyperpigmentation and both palmar and solar keratosis.

Heavy metal toxicity: Cadmium

Cadmium is a silver-white metal and soft in texture with the symbol Cd and atomic number 48. In nature, it is not found alone but in combination with oxygen (CdO), sulphur (CdS) and chlorine ($CdCl_{2)}$. Zinc and cadmium occupy the same column (2B) of the periodic table and also share many similar properties. The basis of the chemistry of cadmium in an aqueous solution indicated that its toxic nature is due to its bivalent cation (Cd^{2+}). The regulatory limit of Cd in agricultural soils is about 100 mg/kg soil [20]. The concentration of Cd greater than 5 ppm shows the toxic effect on animals and Cd poisoning is common in ruminants [4,14]. Cd is highly resistant to corrosion primarily in alkaline and seawater environments. High thermal and electrical conductivity and low melting temperature of Cd make it used in batteries, alloys, electroplating welding and nuclear fission application. It is estimated that nearly about 20000 metric tonnes of Cd is produced worldwide in 2005 [24].

Sources of Cadmium toxicity

Both natural and anthropogenic activities are responsible for Cd emission and pollution of the environment. The natural emission of Cd takes due to forest fires and volcanic eruptions. It is reported that the earth's crust contains 0.1 to 0.5 ppm and is mainly contributed by sedimentary rocks. Whereas man-made activities contribute 3 to 10 times more Cd which is mainly from cadmium batteries, pigmented plastics, Cd coated PVC pipes and ceramics. Moreover, Cd is the major by-product of the extraction, smelting and refinery industries. Agriculture soils contaminated by Cd due to long term use of Phosphatic fertilizers, irrigation with poor quality water act as a secondary source of Cd contamination.

Mode of entry of Cd into livestock

The Cd can enter into the animal body through various ways such as grazing of cattle on Cd contaminated areas, stall feeding of fodders grown by excess use of P fertilizers and drinking of con-

Air	Ambient air	0.003-0.60 µg/m^3
	Occupational environment	2-50 µg/m^3
	Tobacco smoke	0.5-2 µg/cigarette
Water	Ocean	5-110 ng/L
	Surface water (Rain, River etc)	10-4000 ng/L
	Groundwater	Less than 0.1ppm
Soil	From fertilizers	10-100 µg/kg
Foodstuffs	Vegetables	30-150 ppb
	Meat and fish	5-40 ppb

Table 5: Cadmium contribution from different sources to the atmosphere [24].

taminated water leads to entry of Cd into the body system of livestock and results in accumulation in excess amounts.

Toxicokinetics of cadmium

Absorption and translocation of cadmium

With the exposure of the animal to cadmium, it gets accumulated in the liver and interacts with a low molecular protein called Metallothionein's (MT) resulting in the formation of cadmium-Metallothionein's (CdMT) complexes. These CMT complexes will release into the blood and enters into various tissues and organs of animals. Long term exposure to Cd leads to greater accumulation of Cd in the Kidney especially in the cortical region [24]. Cd can be stored in the liver, kidney, testis, heart, lungs, spleen, thymus and salivary glands. However, nearly 50 per cent of absorbed Cd can be stored in the liver and kidney due to the higher concentration of MT [33].

Mechanism of toxicity of cadmium

Dication of cadmium was antagonistic to several metal ions such as zinc, calcium, selenium, iron, magnesium, manganese and leads to their deficiency, which ultimately alters the morphological and functional properties of different organs [24]. Cadmium also affects homeostasis by forming covalent and ionic bonds with elements like sulphur, oxygen and hydrogen which are major constituents of sulfhydryl groups of several amino acids present in cells [3].

Cadmium interferes with mitochondrial oxidative phosphorylation by binding to the thiol groups of membrane protein and consequently alters the membrane permeability thereby reducing membrane potential, cellular ATP levels and also disturbs the homeostasis of calcium, sodium and potassium which results in the leakage of cytochromes and iron ions from cells leading to increased reactive oxygen species. Cadmium replaces calcium from E-cadherin protein resulting in uncontrolled proliferation, cell death and ends in the development of cancer by the activation of B catenin protein [10].

It is well-established fact that metal as well as metalloids when interacting with DNA causes cancer. Likewise, cadmium inhibits DNA methylation [30] resulting in hypomethylation and extensive production of protein products leading to increased proliferation of cells and malignancies [24].

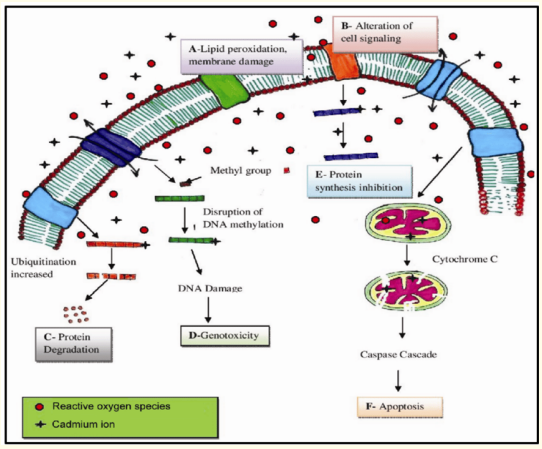

Figure 3: Mechanism of cadmium toxicity at the cellular level [32].

Clinical manifestations of cadmium toxicity

General clinical manifestations of cadmium toxicity in livestock include hypertension, cardiovascular disorders [9], respiratory disorders, anaemia, testicular degeneration and necrosis, joints enlargement, scaly skin, hepatic and renal damage, impeded growth and increased mortality [21], poor mineralization in bones.

Remedies for heavy metal toxicity

There are many remedial measures to reduce heavy metal toxicity in animals. The first option is the provision of alternative water containing low or safe limits of metals. This can be achieved by constructing a rainwater harvesting system that helps in recharg-

Animal species	The toxic dose of Cadmium	Effect Observed
Cattle	A diet containing 5-30 mg of Cd/kg^{-1}	Decrease in performance of cattle
	A diet containing ≥ 30 mg of Cd/kg^{-1}	Disorder of cattle health
Sheep	A diet containing ≥ 40 mg of Cd/kg^{-2}	Animals presenting parakeratosis, reduction in appetite, body weight gain and testicle degeneration
	A diet containing 40-60 mg of Cd/kg^{-2}	Increasing Zn concentration in Liver and Kidney

Table 6: Toxic dose of cadmium and its effects observed on cattle and sheep [22].

ing groundwater and also reduces the concentration of heavy metals to a safer level in groundwater. There are several other methods for the removal of heavy metals from water which are based on several principles of coagulation-precipitation, adsorption-based methodologies, ion-exchange, and reverse osmosis based on membrane separation technologies [11].

Coagulation and precipitation method

In this method, certain coagulants like alum ($Al_2(SO_4)_{3)}$, ferrous sulphate ($FeSO_4$) are used for the removal of heavy metals from groundwater by forming flocs. It is a potential method for the removal of heavy metals (As and Cd) from the different water sources by agglomeration of particles on the positively charged metal ions. pH is the major factor that affects the coagulation process, generally, a pH 5-7 is optimum for efficient coagulation.

Adsorption-based techniques

It is one of the most cost-effective and easy techniques used for both the small- and large-scale removal processes of heavy metal. Whereas heavy metals from water can be removed by adsorption process onto the iron-coated sand, granulated ferric hydroxide and activated carbon [11]. The rate of adsorption mainly depends on pH and the presence of co-existing elements like phosphate, silicate, calcium and bi-carbonate reduce the rate of adsorption of heavy metals. Under the optimum pH of water, amorphous iron and aluminium oxyhydroxides absorb heavy metals to a greater extent due to their larger surface area. The heavy metal removal efficiency of the adsorption-based technique may vary from 23 to 96 per cent depending upon the kind of adsorbent used and conditions [11].

Ion-exchange method

Ion exchange involves the usage of resins that are synthetic and composed of polystyrene cross-linked with divinylbenzene with a functional group attached through covalent bonding. Several anion resins are available which can replace heavy metals from solutions. Descending order of affinities of some of the anions with strong anion resins as follows

$CrO4^{2-} >> SeO4^{2-} >> HSO^{4-} > NO^{3-} > Br- > HAsO4^{2-} > SeO3^{2-} > HSO3^{3-} > NO^{2-} > Cl^-$

Membrane or Reverse osmosis process

In the reverse osmosis process, high-pressure membranes (75 -250 psi) like nanofiltration are used for the efficient removal of heavy metals. These membranes are very selective to a few ions and permit them to pass through them whereas certain ions are excluded or rejected. These membranes contain a pore size equal to the size of metal ion and facilities its removal [15].

Bioremediation

It is the newly emerging, innovative and most effective technique for efficient management of heavy metal toxicity. It involves the usage of green plants to remove the pollutants from the soil and this process is known as phytoremediation. Aquatic plants are widely used for the removal of arsenic from water bodies. Certain plants can be used to accumulate high concentrations of toxic elements in their vegetative parts and this process is known as Phyto filtration. A study (5) reported that *Pteris vittata* (Chinese brake fern) accumulated the highest levels of arsenic in their aerial tissues. The field crops such as sunflower, Indian mustard, maize, grasses (ryegrasses and prairie grasses) are also used in phytoremediation [11].

Summary and Conclusion

The present paper reviewed the heavy metal toxicity of As and Cd, possible source of contamination and its concentration in different feedstuffs, chemical fertilizers and concentrated feeds. It also highlighted the route of entry, absorption, mechanism of action, clinical manifestations in dairy animals along with remedial

measures to control toxicity in water and soil by different methods such as coagulation-precipitation method, adsorption-based techniques, membrane or reverse osmosis process, ion exchange method and bioremediation techniques.

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