

Arsenic, Cadmium, Lead and Mercury as Undesirable Substances in Animal Feeds

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Abstract

Toxic mineral elements occur naturally in the environment as a result of natural causes, as well as industrial and agricultural practices. Among existing toxic mineral elements, the most important are arsenic, cadmium, lead and mercury, which are harmful to animals' health. This review provides evidence on the occurrence of these four toxic mineral elements in the environment and potentially in animal feeds, where considered as undesirable substances, as well as their bioavailability and their effects in animals.

Keywords: animals, arsenic, cadmium, feed, health, lead, mercury

1. Introduction

All minerals can cause toxicosis in animals, when consumed in large quantities [1]. The margin of safety between the minimum amount required to animal feed and the amount that causes adverse effects in animal health varies for different minerals, depending on prevailing conditions.

However, there are many minerals that do not participate in any known function of the animal body and, in fact, are harmful-toxic. Today, environment, plants, animals and humans are exposed to high levels of these toxic minerals, and even higher than ever historically recorded. This is due to their industrial use, and to the without limitation burning of coal, gas and oil, but also to the incineration of waste materials that takes place around the world. Thus, the toxic minerals are now everywhere, participating in a perpetual food chain and affect "everyone and everything" on the planet, being a major cause of disease, aging, and

even birth defects. Among existing toxic mineral elements, the most important are arsenic, cadmium, lead and mercury, which are harmful to animals' health [2].

The objective of this review study is to identify some data on the presence of these four toxic minerals in the natural environment and in feedstuffs, where they are undesirable substances, as well as on their bioavailability and their effects in animals.

2. Toxic mineral elements

2.1. Arsenic (As)

Arsenic (As) is found in the natural environment, being present in soil, groundwater and plants. Arsenic appears in both inorganic and organic compounds, differing in their physical and chemical properties [3, 4, 5]. Areas of our planet with a significant presence of inorganic arsenic have been identified, particularly in Asia and other non-European countries. In Europe, the levels of arsenic in the environment are rather low, with the exception of some areas with particular geological formation or industrial process. The inorganic and

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organic arsenic compounds differ significantly in their toxicity, since the organic arsenic compounds exhibit very low toxicity [4]. Consequently, the potential adverse effects of arsenic to animal and human health are determined by the amount of inorganic arsenic present in food. Drinking water may contain significant amounts of inorganic arsenic, while significant source of arsenic in the diet of human and animals have been identified to fish and other marine organisms, as well as their products. However, generally on marine animal organisms, especially fish, arsenic is present predominately (99%) in the organic forms of arsenobetaine and arsenocholine, which is virtually non-toxic. The organic arsenic compounds have been used as feed additives to control diseases and increase body weight (BW) in pigs and poultry since the mid 1940's and are still used today in various countries [4, 6]. The transport of inorganic arsenic in edible tissues of mammals and birds is generally low, and, thus, foods derived from these tissues contribute only insignificantly to the possible intoxication of human.

The inorganic and organic compounds of arsenic have different bioavailability. Several studies in rats, mice and humans show that inorganic compounds of arsenic, present in drinking water, are rapidly and nearly completely (about 95%) absorbed after ingestion [5]. However, the absorption of ingested inorganic arsenic varies, depending on the solubility of the arsenical compounds (the more water soluble the compound, the greater its absorption), the presence of other food constituents and nutrients in the gastrointestinal tract, and on the food matrix itself [4, 5]. There are also significant differences in bioavailability among the various organic compounds of arsenic. The organic compounds of pentavalent arsenic are absorbed in a significant extent from the gastrointestinal tract of rodents, swine and humans (>40%, 17-33% and 75-80% of ingested dose, respectively), while the organic compounds of trivalent arsenic are generally poorly absorbed [5].

In the bloodstream, arsenic is distributed between the plasma and the erythrocytes, in which it is bound to the globin of hemoglobin. The relative amounts in each compartment depend on the valency and dose of arsenic administered, as well as the species of animal [4, 5]. Then, all the inorganic and organic arsenic compounds

accumulate to various tissues (higher to lower concentration: kidneys > lungs > urinary bladder > skin > blood > liver) [5]. The concentration of arsenic decreases rapidly in various tissues of the body, after ingestion ends. However, several weeks later, arsenic is translocated to hair, nails and skin because of the high concentration of sulfur-containing proteins in these tissues. Furthermore, arsenic readily passes through the placenta in mammals, including humans, resulting in similar exposure levels in both the foetus and the mother. Arsenic and its metabolites are readily excreted in urine and bile, while in contrast, very little arsenic is excreted in breast milk [3, 4, 5].

Suttle [2] reported that arsenic is an essential element for the animal organization, when received in minimal doses. Specifically, he reported that when goats received <35 mg As/kg dry matter (DM) of diet exhibited impaired growth, adverse effects on the reproductive system and abortions, as well as reduced milk production compared to goats fed with 350 mg As/kg DM. These experiments were repeated 13 times, leaving little doubt that arsenic is an essential element for goats in the chosen highly purified, roughage-free diet [2].

It is generally considered that trivalent arsenic compounds are more toxic than the pentavalent forms, at least at high doses. Oral exposure to inorganic arsenic adversely affects almost every system of the animal, including cardiovascular, respiratory, gastrointestinal, hematological, immune, reproductive, and nervous systems [3, 5, 7]. Moreover, inorganic arsenic has been shown to be embryotoxic and teratogenic in experimental animals, and in contrast to humans, where the carcinogenic potential is clearly evident, studies in experimental animals have usually failed to demonstrate increased tumour incidences following chronic oral exposure to inorganic arsenic, with the basis for the lack of tumorigenesis in animals not known yet [5].

In contrast to inorganic arsenic compounds, organic compounds, including arsenobetaine, arsenocholine, trimethylarsine and arsalinic acid, are toxic only at very high doses [4, 5, 7]. Organic arsenic compounds that are used as feed additives in pigs and poultry diets can cause intoxication in these animals, when the concentration of arsenic compounds is 2-10 times higher than the recommended dose, which is usually 100 mg/kg complete feed [7].

The maximum content of arsenic in complete feed has been set by the European Union at 2 mg/kg feed (with 12% moisture) for all animal species and 10 mg/kg for fish and fur animals [8]. The US NRC reported that in cattle the maximum tolerable dose of arsenic is 50 and 100 mg/kg diet for inorganic and organic arsenic compounds [6], respectively, and in goats is 30 mg/kg diet [9]. The toxic dose for oral sodium arsenite (NaAsO_2) is 6.5 mg/kg BW in horses, 7.5 mg/kg BW in cattle, 11 mg/kg BW in sheep, and 2 mg/kg BW in pigs, while for arsenic trioxide (As_2O_3) is 7.5-11 mg/kg BW in pigs and 33-55 mg/kg BW in horses, cattle and sheep [3]. In contrast to inorganic arsenic, in pigs treated with 100 mg arsanilic acid/kg of diet for 6 weeks, only a reduction in food intake was noticed, whereas administration of 1 g arsanilic acid/kg of diet resulted in clinical signs of toxicity [4].

2.2. Cadmium (Cd)

Cadmium (Cd) occurs naturally in the environment in its inorganic form as a result of volcanic emissions and weathering of rocks. In addition, anthropogenic sources have increased the background levels of cadmium in soil, water and living organisms. It is used in many technological applications and released into the environment via the smelting of other metals, the burning of fossil fuels, the incineration of waste materials, and the use of phosphate and sewage sludge fertilizers. Both natural processes (such as volcanic emissions and weathering of rocks) and anthropogenic activities can contribute to the contamination by cadmium of the environment and consequently of the food chain [10, 11]. Increases in cadmium levels in soil result in an increase in the uptake of cadmium by plants, although the extent to which this happens will depend on the soil pH, plant species and the part of the plant, as well as other soil characteristics. Moreover, edible free-living food such as shellfish, crustaceans and fungi are natural accumulators of cadmium.

Cadmium has no known biological function in animals and humans, but mimics other divalent metals that are essential to diverse biological functions [10, 11]. Cadmium was found to be competitive with zinc and copper, and to a lesser extent to iron [1, 6]. It can cross the various biological membranes by different mechanisms (e.g. metal transporters) and once inside the cells

binds to ligands with exceptional affinity (e.g. metallothioneins) [10], thereby reducing the absorption of copper and, to a lesser extent, of zinc [6]. Especially, the liver and kidneys contain metallothioneins, which accumulate cadmium throughout the animal life. However, cadmium is not easily cleared by the cells and the poor efficiency of cellular export systems explains the long residence time of this element in storage tissues such as the intestine, the liver and the kidneys [10]. Cadmium absorbed into the body (0.5-7% of ingested amount, depending on the animal species) is eliminated very slowly, with a biological half-life estimated to be 10-30 years [10, 11]. Perturbation of calcium, zinc or iron homeostasis plays a key role in the toxicological action of cadmium that involves a general threat to basic cellular functions [11].

However, the US NRC [9] reported that cadmium is a necessary element for the animal organization, when received in minimal doses. Specifically, NRC reported that goats fed with <15 μg Cd/kg DM of diet exhibited impaired growth, myasthenia, reduced milk production, and shortened life span when compared to goats supplemented with 250 μg Cd/kg DM of diet.

The intoxication of animals by cadmium is rare [3]. However, when that happens, cadmium is toxic to all animal species, and is accumulated in the kidney and to a lesser extent in liver. Cadmium exposure has been associated with nephrotoxicity, osteoporosis, neurotoxicity, carcinogenicity and genotoxicity, teratogenicity, and endocrine and reproductive effects [10, 11]. In general, clinical symptoms of cadmium toxicity in animals include kidney and liver damage, anaemia, retarded testicular development or degeneration, enlarged joints, scaly skin, and reduced growth and increased mortality [1, 3, 10]. Manifestation of toxicity varies considerably, as depending on dose and time of exposure, species, gender, and environmental and nutritional factors. Subsequently, large differences exist between the effects of a single exposure to a high concentration of cadmium, and chronic exposures to lower doses [10].

The maximum content of cadmium in complete feed has been set by the European Union at 0.5 mg/kg feed (with 12% moisture) for all animal species, 1 mg/kg for ruminants and fish and 2 mg/kg for dogs and cats [8]. Many of the data on the toxicity for animals refer to studies in which

relatively high doses were administered parenterally or orally for a short period [10]. However, of much greater importance are studies that investigated the adverse health effects related to chronic exposure at levels regularly occurring in feeds. In most of the domestic animal species, it is assumed that 5 mg/kg dietary cadmium (5 mg Cd/kg feed) is the level at which gross clinical symptoms are most likely to commence, provided an otherwise adequate diet is offered [10]. Diets containing from 5 to 30 mg Cd/kg of diet generally decrease animal performance by interfering with copper and zinc absorption, resulting in symptoms usually associated with copper and zinc deficiency [6]. Diets containing more than 5 mg Cd/kg can cause copper concentration in liver to decline. Ruminant diets containing more than 30 mg Cd/kg have produced anorexia, reduced growth, decreased milk production and abortion [6]. Moreover, chronic cadmium intoxication has been observed in calves receiving daily 18 mg Cd/kg BW, in sheep receiving daily 60 mg Cd/kg of diet for 137 days, and in pigs receiving daily 50 mg Cd/kg of diet for 42 days [3].

However, minimum toxic levels or maximum safe dietary concentrations cannot be estimated with any precision, since cadmium disposition is significantly influenced by dietary interactions with zinc, copper, iron and calcium. Thus, in some cases, concentrations of cadmium as low as 1 mg/kg in the diet or drinking water did induce adverse effects in animals. These effects included renal function impairment, hypertension, disturbance of trace mineral metabolism (copper, zinc and manganese), and acute degenerative damage in the intestinal villi [10].

2.3. Lead (Pb)

Lead (Pb) occurs naturally in the environment, but its industrial use (e.g. mining, smelting, processing, use in plumbing solders and alloys, pigments, batteries, ceramics, etc.) has resulted in increased levels in soil, water and air [6, 12]. In the past, leaded fuel was important contributor to lead in the environment. However, with the introduction of unleaded fuel in the mid 1980's, lead has considerably decreased in the environment. Lead accumulation in soils and surface waters depends on many factors, including pH, mineral composition, and amount and type of

organic material. Lead in soil is transferred to food crops.

Animal exposure to lead can occur via food, water, soil, dust and air. Lead exists both in organic and inorganic forms [12]. In the environment, inorganic lead predominates over organic lead, while exposure to the latter is generally limited to occupational settings. Organo-lead compounds, such as tri-alkyl-lead and tetra-alkyl-lead compounds, are more toxic than inorganic forms of lead. To some extent, organic lead compounds are metabolised to inorganic lead both in humans and in animals.

Absorption of lead from the gastrointestinal tract depends on host characteristics and on the physicochemical properties of the ingested material [12]. Adult ruminants absorb a 3-10% of ingested lead, while elevated dietary calcium, phosphorous, iron, zinc, fat and protein decrease the absorption and retention of lead [6, 9]. Young animals tend to be more susceptible to lead intoxication than adults [6], because they have a higher rate of absorption of lead (90% vs. 10%). Lead containing metallo-proteins and peptides are then transferred to soft tissues (mainly liver and kidneys) and bones, where lead accumulates with age [12]. From the skeleton, it is released gradually back into the blood stream, particularly during physiological or pathological periods of bone demineralisation such as pregnancy, lactation and osteoporosis, even if lead exposure has already ceased [6, 12]. Calcium and phosphorus supplements delay the release of lead from the skeleton when exposure to lead has ceased [2]. In addition, lead can be transferred from the mother to the foetus in utero and to the newborn animals via milk feeding [6, 9]. Lead is excreted primarily in urine and faeces, half-lives for lead in blood and bone are approximately 30 days and 10 to 30 years, respectively [12].

The US NRC [9] reported that retarded growth, disturbed iron metabolism, anaemia, and impaired lipid metabolism were observed in animals fed diets containing <200 µg Pb/kg DM, suggesting lead as an essential element.

Lead is one of the commonest poisonings in farm animals [1, 3, 6]. Lead affects virtually every system in the animal body, including the blood, the cardiovascular, renal, endocrine, gastrointestinal, musculoskeletal, immune and reproductive systems [3, 6, 7, 12]. Nevertheless, the most critical target for lead appears to be the

central nervous system (CNS), particularly the developing brain, where it has the potential to cause impaired cognitive development and intellectual performance in children even at low exposure levels [12]. Moreover, inorganic lead is classified as a carcinogen by the International Agency for Research on Cancer [12].

The maximum content of lead in complete feed has been set by the European Union at 5 mg/kg feed (with 12% moisture) for all animal species [8]. Furthermore, the maximum tolerable level for cattle and sheep was set at 100 mg Pb/kg DM of diet [9], while a single dose of 200 mg Pb/kg BW is lethal to cattle [6].

2.4. Mercury (Hg)

Mercury (Hg) exists in the environment as elemental mercury (metallic), inorganic mercury and organic mercury (primarily methylmercury). Elemental and inorganic mercury released into the air from mining, smelting, industrial activities, combustion of fossil fuels, is deposited to soil, water and thereby to sediments where the mercury is transformed into methylmercury [13, 14]. Methylmercury bioaccumulates and biomagnifies along the food chain, particularly in the aquatic food chain; longlived carnivorous fish and marine mammals exhibiting the highest contents.

Once released into the environment, mercury undergoes a series of complex chemical and physical transformations as it cycles between atmosphere, land, and water. Humans, plants, and animals are routinely exposed to mercury and accumulate it during this cycle, potentially resulting in a variety of health impacts [13, 14]. The toxicity and toxicokinetics of mercury in animals and humans depend on its chemical form. Elemental mercury is volatile and mainly absorbed through the respiratory tract (80%), whereas its absorption through the gastrointestinal tract is negligible. Gastrointestinal absorption of inorganic mercury is in the 10-30% range [13]. Following absorption, inorganic mercury distributes mainly to the kidneys (by 60-90%) and, to a lesser extent, to the liver. It should be also noted that liver and kidneys are the two principal organs for the deposition of inorganic mercury in fish. The critical effect of inorganic mercury is renal damage. In animals, as in humans, methylmercury and its salts are readily absorbed in the gastrointestinal tract (>80%) [13, 14]. Absorbed methylmercury is widely distributed to

all tissues, although the largest deposition occurs in the kidney. The elemental and methylmercury, unlike inorganic mercury, is able to cross the blood-brain and the placental barriers. As a consequence, the nervous system is the primary site of toxicity in animals and humans [9, 13, 14]. Mercury has affinity for sulfhydryl groups and cysteine-rich molecules such metallothionein, from which it can interact with zinc and cadmium metabolism [9]. Organic mercury contaminants entering the animal body are converted to Hg^{++} by cleavage of the carbon-mercury bond, with subsequent metabolism occurring via the oxidation/reduction cycle. This occurs in the rumen and the intestine, where it involves the bacterial flora, but also in red blood cells and tissues. However, the rate of demethylation is generally very slow [13, 14].

The main pathway of excretion of inorganic mercury is via the urine, faeces (80%), milk (0.2%) and the exhalation as elemental mercury [13, 14]. The half-life of the absorbed Hg^{++} is approximately 40 days in humans and 78 days in goats. The major part of the excretion of methylmercury is by the fecal route via the bile (about 90%), while milk (1.2%), egg (<1%), saliva, sweat, hair and feathers have been identified as other elimination routes. Much of the methylmercury excreted in the bile is absorbed in the gut, producing an enterohepatic circulation of methylmercury [13, 14]. Methylmercury, however, due to the demethylation undergone in the body (in red blood cells and tissues), and the decomposition undergone by the bacterial flora of the rumen and intestine, and thus its conversion to inorganic mercury, which as already mentioned is absorbed only by 10-30% by the gastrointestinal tract, is eventually excreted from the body [13, 14]. The half-life of methylmercury is approximately 60-80 days in humans, 22 days in goats, 4-49 days in poultry and 202-516 days in fish [13].

Mercury toxicity is not common. However, when that happens, mercury affects virtually every system in the animal body, including renal, nervous, gastrointestinal, respiratory and musculoskeletal systems, while mercury exposure has been associated with carcinogenicity and teratogenicity [3, 6, 7, 9, 13]. Mercury is also embryocidal [7]. In humans and animals, effects on neurological development have been observed in children of mothers and foetuses of dams

exposed to methylmercury in the diet [13, 14]. The organic mercury compounds primarily affect the nervous system and clinical signs are similar to those seen in calves with polioencephalomalacia: listlessness, incoordination, progressive blindness, and convulsions [6]. However, animals poisoned by organic mercury compounds do not respond to thiamine.

The maximum content of mercury in complete feed has been set by the European Union at 0.1 mg/kg feed (with 12% moisture) for all animal species, 0.2 mg/kg for fish and 0.3 mg/kg for dogs, cats and fur animals [8]. The most sensitive domestic animal species to methylmercury toxicity are cats and mink, while new-born animals (calves, chickens) are more susceptible to methylmercury intoxication as compared to adults [13]. The US NRC reported that in cattle the suggested maximum tolerable concentration of dietary mercury in organic or inorganic form is 2 mg/kg [6]. Moreover, mercuric chloride (HgCl₂) is highly poisonous, the toxic dose for horses and cattle being about 8 g and for sheep 4 g, while a level of 6 mg organic mercury/kg of diet has been recorded as causing deaths in pigs within 5 days [3]. It is also known that the addition of selenium or vitamin E to the diet provides some protection against mercury toxicity [9].

3. Conclusions

Arsenic, cadmium, lead and mercury are toxic mineral elements, harmful to animals' health. Feeds should be continuously monitored to ensure that concentrations of these four toxic mineral elements that possibly exist are below the maximum level that has been set by the European Union.

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