Review

Mineral element and heavy metal poisoning in animals

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Mineral elements are essential to animal health, survival and production because they are part of physiological, structural, catalytic and regulatory organism functions. Therefore, they should be present in diet. However, these minerals when ingested in excessive doses due to errors in balancing mineral supplements and/or complete ration, intake of plants with high mineral concentration, resulting from addition of fertilizers, herbicides, insecticides and fungicides in pasture or tillage where plants and/or grains will be used to feed animals, decomposition of urban and industrial wastes, leaks and accidental spills of pollutants may result in accumulation of toxic mineral elements in the environment poisoning the animals and may lead them to death. However, toxic doses, physiological changes during poisoning, symptoms and mineral concentration in tissues of poisoned animals to confirm diagnosis are not completely known. Thus, this study reviews mineral element doses that some authors considered toxic for animals intake, as its concentration in tissues of poisoned animals and its physiological effects, symptoms, diagnostic procedures and treatment for poisoning by cadmium, lead, copper, chromium, iodine, manganese, molybdenum, selenium and zinc.

Keywords: Cadmium, lead, copper, chromium, manganese, molybdenum, selenium, zinc.

INTRODUCTION

Mineral elements are essential for animal health, survival and production due to their participation in physiological, structural, catalytic and regulatory functions of animal organism (Underwoood and Suttle, 2001). Thus, mineral should be part of a balanced diet. However, when these minerals are ingested in excessive doses by animals, they may cause acute poisoning, that occurs soon after ingestion, or may cause chronic poisoning, when animals ingest toxic doses constantly but at lower concentrations than those that cause acute poisoning, which can lead them to death.

Ingestion of excessive mineral doses by animals can occur on several ways, as: mistake in balancing mineral supplements and/or complete feed, intake of plants that have high mineral concentration or it can be still obtained by use of fertilizers, herbicides, insecticides and fungicides on pasture or tillage where plants and/or grains will be used for animal feed. Moreover, decomposition of urban and industrial wastes, leaks and accidental spills of pollutants may result in accumulation

of toxic mineral in the environment (Pereira, 2001; Radostits et al., 2002).

However, toxic doses, physiological changes during poisoning, symptoms and mineral concentration in tissues from poisoned animals to confirm diagnosis are not completely known yet. In this revision, were described the mineral doses that authors considered toxic to animals by ingestion and its concentration in tissues of poisoned animals, and its physiological effects, symptoms, diagnostic procedures and treatment for poisoning by cadmium, lead, copper, manganese, molybdenum, selenium and zinc in cattle, sheep, goats, horses and pigs.

CADMIUM POISONING

Cadmium (Cd) is a mineral element highly toxic to animals and humans (NRC, 2001; Roman et al., 2002; Patra et al., 2006; Yu et al., 2006; Newairy et al., 2007; Swarup et al., 2007; Djukić-Ćosić et al., 2008; Stanevičinė et al., 2008) and not essential to physiological and biochemical functions (El-Sharaky et al., 2007; Djuić-Ćosić et al., 2008).

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Table 1. Toxic dose of cadmium to cattle and sheep.

Animal specie	Toxic dose of cadmium	Effect observed
Cattle	Diet containing 5 to 30 mg of Cd/Kg[1]	Decrease in performance of cattle
	Diet containing ≥ 30 mg of Cd/Kg[1]	Disorder of cattle's health
Sheep	Diet containing > 40 mg of Cd/Kg of DM[2]	Animals presenting parakeratosis, reduction on appetite, body weight gain and testicle environment
	Diet containing 5 to 60 mg of Cd/Kg of DM[2]	Increased Zn concentration in liver and kidney

[1]NRC (2001); Underwood and Sutle (2001b)[2].

Cd is accumulated in environment by industrial pollution (Patra et al., 2006; Swarup et al., 2007; Stanevičinė et al., 2008) which is responsible for soil contamination and also contaminates pasture (Miranda et al., 2005; Patra et al., 2005; Swarup et al., 2005; Yu et al., 2006; Swarup et al., 2007), because some plants can accumulate this mineral, so this toxic element is ingested by animals grazing these plants (Yu et al., 2006; Grant et al., 2008) or seeds (whole or as meal) (Wu et al., 1999; Zheng et al., 2001; Wang et al., 2002; Yu et al., 2006). However, Cd accumulation and distribution in plant is influenced by several factors as genetic, size, root morphology, association and colonization between root and microorganisms, cell membrane transport, intracellular mineral binding site and accumulation in root (Harris and Taylor, 2004; Ishikawa et al., 2005; Arao and Ishikawa, 2006; Grant et al., 2008).

Cadmium is present in various materials as anti-corrosive coating (Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002), pigments (specially red and yellow) (Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002), stabilizers (Istomin et al., 1999; Kumar et al., 2000; NRC, 2001; Roman et al., 2002), PVC products (Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002), material galvanization, battery components (nickel-cadmium) (Istomin et al., 1999; Kumar et al., 2000; NRC, 2001; Roman et al., 2002), eliminated gas from motor vehicles (Taylor, 1997; Roman et al., 2002), phosphate fertilizers, pesticides (Taylor, 1997; Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002), plastics (Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002) and glass (Istomin et al., 1999; Kumar et al., 2000; Roman et al., 2002). These cadmium contamination sources are constantly introduced into environment (soil, water and air) and can poisoning animals when ingested and/or inhaled increasing this mineral concentration in bloodstream (McDowell, 1992; Roman et al., 2002; Miranda et al., 2005; Patra et al., 2005; Swarup et al., 2005; Swarup et al., 2007).

In animal diets, the maximum concentration of cadmium tolerated is 0.5mg/kg (McDowell, 1992; NRC, 2001). Cadmium dose considered toxic for cattle is described in Table 1.

Studies have shown that cadmium poisoning mechanism is dependent on organism mineral inflow, ingested dose, metal chemical form, during of exposure to mineral element, animal specie and age (Kuester et al., 2002; Stanevičinė et al., 2008)

When cadmium is ingested, it is absorbed by intestinal cells and transported by blood flow to the liver. In liver, this mineral element induces metallothionein synthesis, a protein that is envolved in detoxification of heavy metals (Groten and Blanderen, 1994; Klaassen and Liu, 1997; McKenna et al., 1998; Sogawa et al., 2001; Roman et al., 2002; Smalinskienė et al., 2005; Djukić-Ćosić et al., 2008). Thus, when cadmium bound to metallothionein it forms a toxicologically inert complex (Klaassen et al., 1999; Nordberg and Nordberg, 2000; Jacob et al., 2002; Djukić-Ćosić et al., 2008; Stanevičinė et al., 2008). Therefore, this protein removes cadmium from hepatocytes forming a cadmium-metallothionein complex that is released into bloodstream and filtered by kidney glomeruli, where it can be degrade by lysossome enzymes from kidney tubular cells (Squibb and Fowler, 1984; Roman et al., 2002). However, metallothionein action is limited (Habeebu et al., 1998; Stanevičinė et al., 2008) and when animals ingest excessive doses of Cd, it can accumulate in organism during decades causing subacute, acute or chronic poisoning (Djukić-Ćosić et al., 2008) which cause severe damage to various organs as liver (Aranha et al., 1994; Roels et al., 1999; Ikeda et al., 2000; Roman et al., 2002; Alonso et al., 2004; Djukić-Ćosić et al., 2008), cause morphological and functional changes (Dehn et al., 2004; Newairy et al., 2007), kidney (Aranha et al., 1994; Roels et al., 1999; Ikeda et al., 2000; NRC, 2001; Roman et al., 2002; Alonso et al., 2004; Djukić-Ćosić et al., 2008), lung (Djukić-Ćosić et al., 2008), bones (Blottner et al., 1999; Uemura, 2000; Roman et al., 2002; Djukić-Ćosić et al., 2008), nervous system (Groten and Blanderen, 1994; Roman et al., 2002), testis (Blottner et al., 1999; Roman et al., 2002; Djukić-Ćosić et al., 2008), intestine (Groten and Blanderen, 1994; Roman et al., 2002), skin (Blottner et al., 1999; Roman et al., 2002) and blood (Roels et al., 1999; Ikeda et al., 2000; Roman et al., 2002).

In mice, cadmium poisoning inhibits protein synthesis, this inhibition is dependent on poisoning duration and Cd ingested dose (Ivanov et al., 2005), by reducing tRNALeu synthesis and activity and increase of leucyl-tRNA sintetase activity in liver (Ivanoviene et al., 2004; Ivanov et al., 2005; Stanevičinė et al., 2008). This increase of leucyl-tRNA sintetase activity probably occurs to compensate partial tRNALeu activity. However, activation mechanism of leucyl-tRNA sintetase is still unknown (Stanevičinė et al., 2008). Cd affects nucleic acid by inducing oxidation (Kasprzak, 2002; Stanevičinė et al., 2008) or by inhibit repair mechanisms (Hartwitg and Schwerdtle, 2002; Stanevičinė et al., 2008).

Cd also impairs adhesion between cells, energy metabolism, DNA (Shimoda et al., 2001; Waisberg et al., 2003; Smalinskienė et al., 2005; Newairy et al., 2007). In addition, it severely interferes on cell metabolism resulting cell death in mice (Kim et al., 2003; Ivanov et al., 2005). This mineral element induces two types of cell death: apoptosis and necrosis, depending on cell type (Habeebu et al., 1998; Ivanov et al., 2005). In mice hepatocytes after 8 to 24 hours of Cd poisoning there is a increase and a decrease, respectively, of protein synthesis in mice hepatocytes (Smalinskienė et al., 2005), apoptosis after 9 to 14 hours and necrosis after 14 to 48 hours (Habeebu et al., 1998; Ivanov et al., 2005; Smalinskienė et al., 2005).

Cd increases reative oxygen species (ROS) concentration by inhibiting action of superperoxido dismutase, catalase and glutathione peroxidase enzymes which act on antioxidant system of liver cells (Sarkar et al., 1995; El-Maraghy et al., 2001; Djuić-Ćosić et al., 2008). Thus, excessive ROS and lipoperoxide (LPO) synthesis cause hepatotoxicity (Stohs and Bargchi, 1995; Stohs et al., 2001; Newairy et al., 2007; Djuić-Ćosić et al., 2008) and also proteins, structure and function of nucleic acids (Newairy et al., 2007).

Clinical symptoms presented by cadmium poisoned animals are reduction in growth and weight gain (McDowell, 1992; NRC, 2001; Stanevičinė et al., 2008), food intake, anemia (McDowell, 1992; NRC, 2001), enlargement of joints, inflammation of liver parenchyma (Habeebu et al., 1998; Stanevičinė et al., 2008; Djuić-Ćosić et al., 2008) and renal changes, less development of testes or testicular degeneration (McDowell, 1992), testicular necrosis (Newairy et al., 2007), abortion (McDowell, 1992; NRC, 2001). Moreover, poisoned animals by cadmium may present tumors (Rojas et al., 1999; Waalkes, 2000; Roman et al., 2002; Waisberg et al., 2003; Ivanov et al., 2005; Newairy et al., 2007), teratogenicity (Roman et al., 2002) because this mineral causes changes in DNA (Hartwig, 1998; Roman et al., 2002) and increase progesterone and 17-β estradiol plasma concentrations. These hormonal changes disturb follicular development and cause difficulty in maintaining pregnancy (Swarup et al., 2007).

Zinc and iron have a protective effect on cadmium accumulation in kidneys, liver and gastrointestinal system by reducing cadmium concentration (Torra et al., 1995; Roman et al., 2002; Alonso et al., 2004) when activate protein synthesis in liver, kidneys and pancreas as metallothionein and HSP which bind to intracellular Zn and Cd and consequently reduce potential toxic effects of cadmium (Suzuki et al., 1990; Smalinskienė et al., 2005). More, Zn protects DNA from Cd damage effects and also cells from apoptosis (Ohkawara et al., 1996; Smalinskienė et al., 2005). Thus, animals deficient in calcium, iron and zinc are more susceptible to be poisoned by cadmium (Alonso et al., 2004).

Administration of selenium to poisoned animals by cadmium has hepatoprotective effect (Newairy et al., 2007) and also protects kidney from damage caused by this mineral (El-Sharakay et al., 2007). Administration of selenium increases selenoproteins activity specially glutathione peroxidase and thioredoxin reductase (Newairy et al., 2007). Glutathione has high affinity for metals forming a complex with thermodynamically stable inert cadmium (El-Sharaky et al., 1987; Newairy et al., 2007) which is excreted by bile, as also reduce formation of free radicals formed in organism of poisoned animal (Gan et al., 2002; Newairy et al., 2007) acting on detoxification of this mineral element (El-Sharakay et al., 2007; Mohanpuria et al., 2007; Newairy et al., 2007).

Administration of diets with high molybdenum concentration reduces cadmium accumulation in sheep organism (Smith and White, 1997; Alonso et al., 2004) and iron prevents signs of cadmium poisoning (Groten et al., 1991; Alonso et al., 2004).

Vegetable have two chemical compounds called phytochelatins and phytic acid that bind to cadmium. Thus, vegetable-based diets reduce cadmium uptake by intestinal cells and also reduce concentration of this mineral in organism (Turecki et al., 1994; Cobbett, 2000; Roman et al., 2002).

Copper and manganese increase cadmium concentration in organism (Jacobs et al., 1983; Roman et al., 2002).

Cadmium dosage in liver, kidney (Table 2) and blood of animals can be a way to evaluate the concentration of this mineral in animals body and also may be a way to diagnose cadmium poisoning, when this element is in high concentration in the body (Gyori et al., 2005; Pain et al., 2005; Patra et al., 2006; Patra et al., 2007).

LEAD POISONING

Lead (Pb) has biological functions in animal body but is highly toxic to animals and humans (NRC, 2001; Roman et al., 2002; Patra et al., 2006; Patra et al., 2007; Swarup et al., 2007), being one of the most danger minerals to animal health, has worldwide distribution and is

Table 2. Concentrations of cadmium ni liver and kidney of cattle and sheep versus mineral concentration in diet (Adapted by Puls (1994) *apud* Underwood and Suttle (2001)

Animal specie	Cadmium concentration on diet (mg/Kg of DM)		Cadmium concentration in tissue (mg/Kg/FW)	
			Liver	Kidney
Cattle and sheep	0.1 to 0.2	Normal	0.02 to 0.05	0.03 to 0.10
	0.5 to 5.0	High	0.1 to 1.5	1.0 to 5.0
	>50	Toxic	50 to 160	100 to 250
Pig	0.1 to 0.8	Normal	0.1 to 0.5	0.1 to 0.10
	1.0 to 5.0	High	1.0 to 5.0	2.0 to 5.0
	>80	Toxic	>13	<270

accumulated in environment by industrial pollution (Patra et al., 2006; Patra et al., 2007; Swarup et al., 2007).

Cattle are the specie which are poisoned more frequently and sheep and horses in lower frequency (Rumbeiha et al., 2001; Strojan and Phillips, 2002; Waldner et al., 2002; Marçal et al., 2005; Swarup et al., 2005; Miranda et al., 2006). Pigs, due to their production system, are less exposed to lead and also are more tolerant to this mineral element than other species, therefore saturnismo also occurs rarely (Radostits et al., 2002; Miranda et al., 2006; Radostits, 2007).

The lead poisoned animal can be considered a risk to public health, since there is an accumulation of this mineral in meat and milk (when animals have blood concentration ≥ 0,20 µg of Pb/mL) for human consumption it may intoxicate them (Waldner et al., 2002; Miranda et al., 2005; Swarup et al., 2005). The European Commission Regulation 466/2001 accepts 0.1 ppm as the maximum tolerable concentration of lead in beef. For drinks and fruits is acceptable up to 0.08 ppm of lead according to US Food and Drug Administration. In mineral mixture, the maximum acceptable concentration of Pb is 10ppm (Malleto, 1986; Marçal et al., 2005).

Animals deficient in calcium, iron and zinc are more susceptible to be poisoned with lead, because there is increased absorption of this mineral element. Administration of calcium, iron and zinc reduce lead toxicity (Alonso et al., 2004).

Chronic lead poisoning usually occurs in animals built around mining and industries that process lead (Dwivedi et al., 2001; Radostits et al., 2002; Swarup et al., 2007). In fact, polluants of these industries are responsible for pastures contamination and consequently increase of this mineral in animal bloodstream (Patra et al., 2005; Swarup et al., 2005; Swarup et al., 2007). However, Waldner et al. (2002) report that between 4-12% of cattle with lead blood concentration considered toxic remain asymptomatic.

The lead sources are food contaminated with automotive oil, pastures near lead smelters and battery factory (Stöber, 1989; Rumbeiha et al., 2001; Radostits et al., 2002; Strojan and Phillips, 2002; Waldner et al., 2002;

Miranda et al., 2006; Patra et al., 2006; Krametter-Froetscher et al., 2007; Patra et al., 2007), ash from wood painted with oil, grease from machines, discarded paint cans, plies (Rumbeiha et al., 2001; Radostits et al., 2002; Strojan and Phillips, 2002; Patra et al., 2005; Miranda et al., 2006; Krametter-Froetscher et al., 2007) and fences, walls, floors, drinkers, feeders and silos which had paint with lead on it that cattle may lick them (Stöber, 1989; Radostits et al., 2002; Strojan and Phillips, 2002; Krametter-Froetscher et al., 2007). Still, other source are pastures on road borders contaminated with high levels of gases from gasoline vehiclesbecause this fuel contains lead tetraetileno (Stöber, 1989; Rumbeiha et al., 2001).

Marçal et al. (2003 and 2005) reported that some mineral mixtures marketed in São Paulo, Mato Grosso, South Mato Grosso and Paraná had high lead concentration, being over the maximum acceptable limit (30ppm) and in some mineral mixtures of South Mato Grosso was found up to limits of 460 ppm of lead, which can cause lead poisoning in animals.

The doses of lead that cause poisoning in animals are described in Table 3 (Radostits et al., 2002).

Lead is absorbed as acetate and carbonate. This absorption is low and may even reach 10 % of intake due to formation of insoluble complexes of lead in gastrointestinal tract that are excreted with feces (Radostits et al., 2002; Waldner et al., 2002).

Lead excretion from the animal body occurs by bile, urine, feces and milk (Stöber, 1989; Rumbeiha et al., 2001; Radostits et al., 2002; Radostits, 2007).

When animals are acutely lead poisoned, this mineral is deposited specially in liver (Rumbeiha et al., 2001; Radostits et al., 2002; Waldner et al., 2002; Miranda et al., 2006; Swarup et al., 2007) renal cortex (Stöber, 1989; Rumbeiha et al., 2001; Radostits et al., 2002; Waldner et al., 2002; Miranda et al., 2006; Swarup et al., 2007), endocrine system (Swarup et al., 2007) and medulla (Radostits, 2007). In chronic poisoning, lead deposition occurs in bones (Stöber, 1989; Waldner et al., 2002; Radostits et al., 2002). In addition to these tissues, lead is also deposited in brain, however, in lower

Table 3. Toxic dose of lead to cattle, horses, pigs, sheep and goats

Animal specie	Toxic dose	Effect observed
Cattle	400 to 600 mg of Pb/Kg of BW[1]	Acute poisoning in Young cattle
	600 to 800 mg of Pb/Kg of BW[1]	Acute poisoning in adult cattle
	6 to 7 mg of Pb/ Kg of BW[1,2]	Chronic poisoning
	200 to 300 mg of Pb/Kg of DM in diet[1]	Chronic poisoning
	Single dose of 200 to 400 mg of Pb/Kg of BW	Calve death after ingestion
	Single dose of 10 to 100 g of lead acetate [2]	Death of adult cattle after ingestion
Horses	100 mg of Pb/Kg of BW[1]	Chronic poisoning
Pigs	33 to 66 mg of Pb/Kg of BW[1]	Chronic poisoning
Sheep	4,5 mg of Pb/Kg of BW[1]	Chronic poisoning
Goats	400 mg of Pb/Kg[1]	Chronic poisoning

[1]Radostits et al. (2002); Stöber (1989)[2].

concentrations compared to other deposition tissues (Radostits et al., 2002; Swarup et al., 2007). With the exception of bones, in other tissues mentioned, lead does not remain deposited for long periods of time, because it is released into bloodstream and may cause chronic lead poisoning in animals (Radostits et al., 2002).

Lead passes the placental barrier in high concentrations and is deposited in fetal tissues (O'hara et al., 1995; Radostits et al., 2002; Waldner et al., 2002), as bones, kidney, liver (O'hara et al., 1995; Radostits et al., 2002) and nervous system due to immaturity of the blood-brain barrier (O'hara et al., 1995; Waldner et al., 2002).

Lead competes with calcium channels and this interrupts cholinergic function by decresing the acetylcholine release and turnover (Suszkiw et al., 1984; Reddy et al., 2003; Swarup et al., 2007), and still exerts an inhibitory effect on acetylcholinesterase interfering in cerebellum functions, which consequently changes motor coordination (Gietzen and Woolley, 1984; Reddy et al., 2003; Swarup et al., 2007).

The effects of lead on rumen microorganisms has not been fully clarified. However, it is assumed that inorganic lead is not absorbed by bacteria and fungi in rumen. However, ion lead is strong to form organic compounds as lead acetate, which is soluble in lipids and organometallic compounds, able to inhibit respiration and growth of rumen microorganisms. This slower microbial growth reduces rate of forage digestion (Strojan and Phillips, 2002).

Pastures containing concentrations of lead at a concentration ≥ 350 ppm may cause lead poisoning in animals (Radostits et al., 2002). However, cattle are capable of detecting this mineral on forage starting at 30 ppm and reduce grazing time due to the adverse effect of acceptability of forage contaminated with lead (Strojan and Phillips, 2002).

The symptoms presented by lead poisoning bovine vary with way of poisoning, which can be subacute, acute or chronic (Stöber, 1989; Radostits et al., 2002; Krametter-Froetscher et al., 2007):

Subacute lead poisoning

Cattle may exhibit the following clinical symptoms: depression (Rumbeiha et al., 2001; Radostits et al., 2002), anorexia, incoordenation and gait and/or circling, muscle twitching, gnashing of teeth, ruminal stasis, constipation and death in 72 to 96 hours after excessive intake of lead (Radostits et al., 2002).

Subacute lead poisoning is the main formo f poisoning by this mineral in sheep, which may present the following clinical symptoms: muscle weakness (Radostits et al., 2002), ataxia (Rumbeiha et al., 2001; Radostits et al., 2002), abdominal pain and convulsing (Radostits et al., 2002).

The subacute poisoning may also cause changes in reproductive system as anestrus, increase parturition interval and abortion (Marçal et al., 2005; Swarup et al., 2007).

Acute lead poisoning

This poisoning occurs when animals ingest large quantities of lead at once (Stöber, 1989; Miranda et al., 2006), being the most frequently form (Ozmen and Mor, 2004; Miranda et al., 2006; Krametter-Froetscher et al., 2007).

Cattle acutely poisoned can present clinical symptoms between 1 to 3 days after ingestion of lead toxic dose (Stöber, 1989), that are: staggering gait (Radostits et al., 2002; Ozmen and Mor, 2004; Krametter-Froetscher et al.,

Table 4. Concentration of lead considered toxic in blood, kidney, liver and bone of ruminants, horses and pigs.

Animal specie	Toxic concentration of lead in tissues (ppm)			
	Blood	Liver	Kidney	Bone
Ruminants	≥ 0.35[2]	10 to 20[2]	25[2]	>75[1]
Pigs	≥ 1.2[2]	40[2]	>25[1]	>500[1]
Horses	≥ 0.35[2]	4 to 7[2]	25 to 250[2]	

Underwood and Suttle (2001b)[1]; Radostits (2007)[2]

2007), walking in cicle (Stöber, 1989; Swarup et al., 2007), muscle twitching mainly in the head, ear and neck (Stöber, 1989; Radostits et al., 2002; Ozmen and Mor, 2004; Krametter-Froetscher et al., 2007), gnashing of teeth (Stöber, 1989; Radostits et al., 2002), progressive incoordination of hindlimbs and after recumbency, ataxia (Stöber, 1989; Ozmen and Mor, 2004; Krametter-Froetscher et al., 2007), difficulty swallowing (Stöber, 1989), salivation (Stöber, 1989; Ozmen and Mor, 2004; Krametter-Froetscher et al., 2007), foaming at the mouth, opisthotonus (Radostits et al., 2002), blindness (Stöber, 1989; Radostits et al., 2002), colic, green diarrhea (Stöber, 1989; Schlerka et al., 2004; Krametter-Froetscher et al., 2007), convulsions (Radostits et al., 2002), tachypnea (Radostits et al., 2002; Ozmen and Mor, 2004; Krametter-Froetscher et al., 2007), tachycardia (Radostits et al., 2002; Ozmen and Mor, 2004; Krametter-Froetscher et al., 2007) and sudden death (Radostits et al., 2002).

Horses acutely lead poisoned may present: anorexia, exacerbated nervous depression (Hoff et al., 1998; Radostits et al., 2002), paralysis, recumbency (Radostits et al., 2002), abdominal pain (Hoff et al., 1998; Radostits et al., 2002) ranging from light to severe and convulsion (Radostits et al., 2002).

Chronic lead poisoning

This poisoning occurs when animals continuously ingest doses just above the tolerable upper limit of lead in diet (Stöber, 1989).

Cattle chronicly lead poisoned may present the following clinical symptoms: opaque hair, thickeningof phalange epiphyses, moderate anemia (Stöber, 1989; Miranda et al., 2006), severe depression, paresis of hyglossal nerve, incoordination, ataxia, muscle twitching, opisthotonus (Radostits et al., 2002), convulsion (Radostits et al., 2002; Gilbert et al., 2005), coma, respiratory failure and death (Gilbert et al., 2005; Radostits et al., 2002), reduction in triiodtironina (T_3) and thyroxine (T_4) concentration, increase in estradiol plasma concentration (Swarup et al., 2007).

In chronic poisoning by lead, sheep presents: paralysis of hindlimbs, difficulty walking, osteoporosis, incomplete flexion of limb joints, abortion and transient infertility (Radostits et al., 2002).

Already, horses may exhibit: harsh, dry and dull hair, weight loss (RADOSTITS et al., 2002), paralysis of pharynx (Hoff et al., 1998; Radostits et al., 2002), regurgitation of food and water through nostrils (Radostits et al., 2002), inspiratory dyspnea, generalized muscle weakness (Hoff et al., 1998; Radostits et al., 2002), stiff joints, colic (Hoff et al., 1998) and may die without showing any symptoms (Radostits et al., 2002).

Diagnostic

The concentration of lead in blood of ruminants, pigs and horses considered normal is 0.05 to 0.25 ppm (Radostits et al., 2002; Swarup et al., 2007).

The determination of lead in blood, kidney, liver, boné and hair of animal suspected of poisoning are done to assess the concentration of this mineral in body as also to diagnose lead poisoning in animals (Gyori et al., 2005; Pain et al., 2005; Ozmen and Mor, 2004; Miranda et al., 2006; Patra et al., 2006; Patra et al., 2007; Radostitts, 2007). The concentration considered toxic in these tissues are described in Table 4.

Lead concentration in bloodstream that can cause death of animals is ≥ 1.0 ppm (Radostits et al., 2002; Swarup et al., 2007). Already in pigs, the concentration considered lead poisoning is ≥ 1.2 ppm (Radostits et al., 2002).

In animals poisoned by lead this mineral concentration in blood may return to normal, but it takes a long period of time. According to Rumbeiha et al. (2001) this can vary from 48 to 2 507 days while for Miranda et al. (2006) this time may be shorter, 68 to 266 days. This variation to return to normal blood concentration of lead (<0.050 mg de Pb/l) is probably due to differences in amount of lead absorbed and size of particles (Miranda et al., 2006).

Differential diagnosis

Lead poisoning in animals has to be differentiated to the following diseases as species affected.

Cattle: poliencephalomalacia (O'hara et al., 1995; Radostits et al., 2002), meningoencephalitis (Radostits, 2007), osteomalacia, fluorosis (Stöber, 1989; Radostits, 2007), rabies (Stöber, 1989; O'hara et al., 1995; Radostits et al., 2002; Radostits, 2007), listeriosis (O'hara et al., 1995), pastures tetany (hypomagnesemia) (Stöber, 1989; Radostits et al., 2002; Radostits, 2007), vitamin A deficiency (O'hara et al., 1995; Radostits et al., 2002), copper deficiency (Stöber, 1989), nervous acetonemia (Stöber, 1989; Radostits et al., 2002; Radostits, 2007) and arsenic poisoning (Radostits et al., 2002).

Horses: laryngeal hemiplegia, encefalmielite virus, rabies, botulism, equine degenerative mieloencefalophaty and chronic upper respiratory disease (Radostits et al., 2002; Radostits, 2007).

Sheep: enzootic ataxia by copper deficiency, polyarthritis, enzootic muscular dystrophy (RADOSTITS et al., 2002) and hepatoencephalopaty caused by toxic plants (Radostits, 2007).

Treatment

Edetate calcium disodium (CaEDTA) has the function to remove lead deposited in tissues of animals poisoned by lead. CaEDTA has to be administered intravenously at a dose of 110 to 220 mg of CaEDTA/Kg of PV for a period of 12 hours by rapid injection of two doses of 110 mg of CaEDTA/Kg of PV with six hours interval daily during three to five days (Radostits et al., 2002; Krametter-Froetscher et al., 2007). Administer CaEDTA with large amount of saline or glucose to increase diuresis (Stöber, 1989; Krametter-Froetscher et al., 2007).

Thiamine chloride, this vitamin reduces lead deposition specially in kidney, liver, central and peripheral nervous system and also increases lead excretion from body of poisoned animals by urine and bile, because this vitamin combined with CaEDTA chelates lead in tissues of poisoned animals. The therapeutic dose for cattle is 25 mg of thiamine/Kg of body weight subcutaneously twice a day and for sheep, 75 mg of thiamine/Kg (O'hara et al., 1995; Radostits et al., 2002; Krametter-Froetscher et al., 2007).

200 to 300 grams of magnesium sulfate orally, in an attempt to interact with magnesium sulfate to form lead sulfate, which precipitates and is excreted in feces (Stöber, 1989; Radostits et al., 2002; Krametter-Froetscher et al., 2007).

Ruminotonia occurs soon after ingestion of materials and/or foods that contain high concentrations of lead (Stöber, 1989).

COPPER POISONING

Copper is an essential mineral element, being part of various enzymes and proteins. However, it is extremely toxic when ingested in excess (Jenkins and Hidroglou, 1989; Sullivan et al., 1991; Steffen et al., 1997; Bailey et al., 2001; Engle et al., 2001; López-Alonso et al., 2005; Blanco-Penedo et al., 2006; López-Alonso et al., 2005a; Christodoulopoulos and Roubies, 2007). Poisoning by this mineral is responsible for economic losses due to mortality of animals (Headley et al., 2008).

Copper is widely distributed in nature, being used in its various forms, and copper sulphate is used in agriculture as pesticides, fungicides and herbicides (Lebre et al., 2005).

Poisoning by copper occurs specially in sheep-producing countries like Australia, New Zealand, United States, Britain and South Africa (Headley et al., 2008).

In Brazil, copper poisoning was reported in South Rio Grande, however, such reports are infrequent because sheep industry in Brazil is not the main economic activity (Headley et al., 2008). With sheep introduction in orchards to reduce cleaning cost and contribute to fertilization by feces and urine, these animals are exposed to copper used in pests periodic control, that makes copper concentration increase in pastures (Ribeiro et al., 2007).

Copper poisoning is a complex problem by having multiple factors that can influence intake, metabolism and copper excretion. Thus, copper poisoning was divided in primary and secondary (Radostits et al., 2002).

Among species, there is variation in susceptibility to copper poisoning, and equine have less susceptibility probably due to tolerate high concentrations up to 800 ppm of copper in diet. Pigs can tolerate up to 250 ppm of copper in diet (McDowell, 1992; Radostits et al., 2002; López-Alonso et al., 2005a). Cattle are relatively tolerant to copper and support up to 100 mg of Cu/Kg of food (Perrin et al., 1990; McDowell, 1992; Bradley, 1993; NRC, 1996; Hoff et al., 1998; Engle et al., 2001; Radostits et al., 2002; López-Alonso et al., 2005; Blanco-Penedo et al., 2006; López-Alonso et al., 2006) and calves tolerance to upper copper dose in milk is unknown (Jenkins and Hidroglou, 1989). However, milk with up to 50 ppm of copper did not caused poisoning symptoms, but when milk had 200 and 500 ppm of copper calve weight gain was reduced (Jenkins and Hidroglou, 1989) and milk with 1,000 ppm lead calves to death 3 to 5 days post ingestion (Jenkins, 1989; Jenkins and Hidroglou, 1989). Already, sheep is the specie that has more susceptibility to copper poisoning (Goonerate et al., 1981; Sullivan et al., 1991; McDowell, 1992; Lewis et al., 1997; Hoff et al., 1998; Engle et al., 2001; Radostits et al., 2002; López-Alonso et al., 2005; Blanco-Penedo et al., 2006; Christodoulopoulos and Roubies, 2007; Headley et al., 2008) specially in intensive system (Goonerate et al., 1981) due to low tolerance to this mineral in diet, tolerate maximum 25 mg of copper/Kg of body weight (McDowell, 1992; Radostits et al., 2002) (5 to 10 µg/g of

total food (Hoff et al., 1998) and still not able to increase mineral excretion by bile (López-Alonso et al., 2005a).

Cattle and sheep are more susceptible to copper poisoning probably due to have lower efficiency to excrete copper. These species synthetize lesser amounts of metalloprotein containing copper such as metallothionein (MT) in relation to animal species that are considered more resistant to poisoning by this mineral (Saylor et al., 1980; López-Alonso et al., 2005; López-Alonso et al., 2005a). Although the role of MT is not totally elucidated (Harrison and Dameron, 1999; López-Alonso et al., 2005a), this enzyme is involved in cell detoxification of copper, ie, copper excretion in bile through the direct pathway of hepatocyte cytoplasm or via hepatolysossomal in which copper is bound to metallothionein in lysossomes to be excreted in bile (Gooneratne et al., 1989; López-Alonso et al., 2005a). Thus, when there is an influx of high concentration of copper in liver, the ability of MT bind to copper and lysossomes to remove this mineral from hepatocyte cytoplasm may be exceeded, and then copper begins to accumulate in a higher rate in other organelles such as mitochondria, in cell membrane and specially nucleus due to the presence of nucleic acids and many proteins that bind copper or then copper can accumulate and remain free in hepatocyte cytoplasm and may poisoning cattle and sheep due to less capacity of excretion and store copper in liver, also cause severe liver damage (Jenkins, 1989; Engle et al., 2001; López-Alonso et al., 2005a).

When copper is in excess binds to albumin forming a complex albumin-copper that is the active toxic fraction. Then it rapidly accumulates within red cells that cause oxidative damage and intravascular haemolysis (Lebre et al., 2005).

Selenium administration inhibits the synthesis of MT which reduces copper ability to bind to hepatocyte cytosol. Copper binds to the fraction of hepatocyte nucleus that consequently reduces biliary copper excretion resulting in accumulation of copper in hepatocyte exposing the animals to a chronic copper poisoning (Alonso et al., 2004).

The stressed animal has an increase in susceptibility to copper poisoning (Lewis et al., 1997; Radostits et al., 2002; López-Alonso et al., 2006; Headley et al., 2008) because the stress promotes release of liver accumulated copper to bloodstream (Lewis et al., 1997).

Animals can poisoning them selves by copper when they ingest it in high concentrations (NRC, 1996; Christodoulopoulos and Roubies, 2007) which may result from administration of mineral mix containing high concentration of this mineral element, ingestion of excessive amounts of mineral containing copper (Jenkins and Hidroglou, 1989; Sullivan et al., 1991; NRC, 1996; Blanco-Penedo et al., 2006; López-Alonso et al., 2006; Headley et al., 2008), copper supplementation by intra-

ruminal bolus administration (Steffen et al., 1997; Yost et al., 2002), administration of injections containing (Bohman et al., 1984; Galey et al., 1991), when animals consume foods containing high concentrations of copper (Sullivan et al., 1991; NRC, 1996; Blanco-Penedo et al., 2006; López-Alonso et al., 2006; Christodoulopoulos and Roubies, 2007) or copper contaminated pasture due to polluting industries (Sedki et al., 2003; Blanco-Penedo et al., 2006; López-Alonso et al., 2006), when they drink pé-de-lúvio containing copper. Moreover, sheep created in association with fruit production can be poisoned after application of fungicide containing copper in the orchard (Hoff et al., 1998; Christodoulopoulos and Roubies, 2007). The Trifolium subterraneum pasture when in favorable conditions for growth can accumulate high concentrations of copper and the animals grazing these plants can be poisoned by this mineral element. Heliotropium europaeum and some species of Senecio spp. produce hepatotoxic alkaloids that alter the hepatocytes functioning and consequently liver concentration of copper increases may cause poisoning (Bradley, 1993).

The copper is accumulated in liver of animals resulting in severe structural and functional change and may cause animal's death (Jenkins, 1989; Sullivan et al., 1991; NRC, 1996; Bailey et al., 2001; López-Alonso et al., 2005; López-Alonso et al., 2005a; Blanco-Penedo et al., 2006; Christodoulopoulos and Roubies, 2007; Headley et al., 2008). In cattle, copper also can accumulate in liver because the capacity of this mineral biliary excretion is limited (LÓPEZ-ALONSO et al., 2005). The distribution of copper in sheep and cattle liver is similar with the highest concentration of this mineral in cell cytosol and nucleus (Kumaratilake and Howell, 1989; López-Alonso et al., 2005).

Animals poisoned by copper had na excessive accumulation of this mineral in liver that cause hepatocyte death by oxidative damage, ie lipid peroxidation of cell membrane, and copper is released bloodstream that consequently increases this mineral concentration in blood, causes hemolysis of red blood cells and its release, denaturation and convertion to methemoglobin. This massive hemolysis in association with hemoglobin depletion causes anemia, jaundice and also carries less oxygen concentration and can lead to animal hypoxia. In addition, may occur hemoglobinuria. Furthermore, with the death of hepatocytes the biliary excretion of bile also is reduced which favors copper accumulation in liver (Sullivan et al., 1991; Bradley, 1993).

Primary copper poisoning

It occurs just when animals ingest excessive amounts of copper salts. The doses of copper which can cause acute

Table 5. Toxic dose of copper to cattle and sheep

Animal Specie	Toxic dose of copper	Effect observed
Cattle	Acute poisoning: in calves 20 to 110 mg of copper/Kg of BW[1,2]	Acute poisoning in calves
	Single ingestion of 200 to 400 g of copper sulfate or 200 mg of copper/Kg of BW[3]	Acute poisoning of adult cattle
	Single dose of 220 to 880 mg of copper/Kg of BW[2]	Death of adult cattle
	Daily ingestion of 3 to 5 mg of copper/Kg of BW[2,3]	Chronic poisoning of adult cattle
	1 to 2 g copper/day[3]	Chronic poisoning of calves
	Ingestion of diet containing 80 mg of Cu/Kg during 60 days	Poisoning of adult cattle
	Ingestion of diet containing 115 mg of Cu/Kg during 91 days[5]	Calve poisoning
	Ingestion of mineral mix containing 328 mg of Cu/Kg[6]	High mortality in dairy cows
Sheep	Single dose of 20 to 110 mg of copper/Kg of BW[2]	Acute poisoning
	Daily ingestion of 3,5 mg of copper/Kg of BW[2]	Chronic poisoning
	Diet with 15 ppm of Pb and without appropiate concentration of molybdenum	Poisoning

[1]López-Alonso et al. (2006); [2]Radostits et al. (2007); [3]Stöber (1989); [4]Du et al. (1996); [5]NRC, 1996; [6]Perrin et al. (1990).

poisoning in animals are described in Table 5 (Radostits et al., 2002). This excessive ingestion of copper by animals can occur in various situations such as: grazing immediately after fertilization, pastures grown on soils containing high concentrations of copper, supply of wheat treated with antifungal drugs containing copper, pasture contaminated by smoke from foundries (Radostits et al., 2002), administration of mineral mix with excessive copper concentration (McDowell, 1992). This poisoning can be acute or chronic.

Acute copper poisoning

It occurs in animals after a short period of excessive ingestion of copper (Blakley et al., 1982; Jenkins and Hidroglou, 1989; Stöber, 1989; Bradley, 1993; Steffen et al., 1997), 1 to 3 days post intake (from a single or a few times) of excessive amounts of coppes salts (Stöber, 1989). The poisoned animals may present the following symptoms: salivation (Stöber, 1989; McDowell, 1992), dehydration (Radostits et al., 2002), depression (Steffen et al., 1997; Radostits et al., 2002), hemoglobinuria (Bradley, 1993; NRC, 1996; Lewis et al., 1997; Radostits et al., 2002; Headley et al., 2008), abdominal pain (Stöber, 1989; McDowell, 1992; Bradley, 1993; Steffen et al., 1997; Radostits et al., 2002), gastroenteritis (Jenkins and Hidroglou, 1989; Steffen et al., 1997; Radostits et al., 2002) with excessive blue-green diarrhea or bloody feces (Stöber, 1989), hypothermia (Radostits et al., 2002), tachycardia (Radostits et al., 2002), jaundice (Bradley, 1993; NRC, 1996; Lewis et al., 1997; Steffen et al., 1997; Radostits et al., 2002; Headley et al., 2008), walking in circle (Steffen et al., 1997; Radostits et al., 2002) reelin walking (Steffen et al., 1997; Stöber, 1989), paralysis

(McDowell, 1992), ataxia (Stöber, 1989; Radostits et al., 2002), dyspnea (Steffen et al., 1997), shock (Stöber, 1989; McDowell, 1992; Radostits et al., 2002) and death (Jenkins and Hidroglou, 1989; McDowell, 1992; NRC, 1996; Radostits et al., 2002).

Chronic copper poisoning

It occurs when animals ingest subtoxic doses of copper (Table 5) for several weeks or months, copper accumulates in liver and animals show no clinical symptoms (pre-hemolytic phase). The accumulation in liver causes necrosis of hepatocytes and suddenly copper is released into bloodstream causing a hemolytic crisis (Blakley et al., 1982; Jenkins and Hidroglou, 1989; Sullivan et al., 1991; Lewis et al., 1997; Steffen et al., 1997; Hoff et al., 1998; López-Alonso et al., 2006) when the animals show the following clinical symptoms: jaundice (Blakley et al., 1982; Jenkins and Hidroglou, 1989; Stöber, 1989; Bradley, 1993; NRC, 1996; Lewis et al., 1997; Steffen et al., 1997; Radostits et al., 2002; López-Alonso et al., 2006; Headley et al., 2008), anemia (Jenkins and Hidroglou, 1989; Stöber, 1989; McDowell, 1992; Bradley, 1993; Headley et al., 2008), anorexia (Blakley et al., 1982; Perrin et al., 1990; Steffen et al., 1997; Hoff et al., 1998), ruminal stasis, abdominal pain (Blakley et al., 1982; Steffen et al., 1997), reduction in milk production and body weight gain (Stöber, 1989; Perrin et al., 1990; López-Alonso et al., 2005;), abortion and infertility (Stöber, 1989; McDowell, 1992), areas of alopecia (Stöber, 1989; Perrin et al., 1990;), pale mucosa (Stöber, 1989), hemoglobinuria (Blakley et al., 1982; Sullivan et al., 1991; Bradley, 1993; Lewis et al., 1997; Radostits et al., 2002; Headley et al., 2008), hematuria

Table 6. Concentration of copper considered toxic in the liver, kidney, feces, serum and activity of gamma glutamyl transferase (GGT) and glutamate dehydrogenase (GLDH) enzymes of cattle, sheep, pigs and goats.

Animal specie	Concentration of copper considered toxic in tissues					
	Liver (mmol/Kg)	Kidney (mmol/Kg)	Feces (ppm)	Blood serum (µmol/L)	GGT (UI/L)	GLDH (UI/L)
Cattle	30.0[2]	0.6-0.8[1]	8 000-10 000[2]	20-25[1]	45-100[1]	12-51[1]
Sheep	7.85[2]	1.25 -1.57[2]		20-25[1]	45-100[1]	12-51[1]
Pigs	95.0[2]	10.0-16.0[1]		40-60[1]		
Goat	6.4-16.0[1]	0.6-0.8[1]		20-25[1]		

Underwood and Suttle (2001c)[1]; Radostits (2007)[2]

(Blakley et al., 1982), hemoglobinemia (Blakley et al., 1982; Stöber, 1989), muscle twitching (Radostits et al., 2002), diarrhea with feces dark green to black (Perrin et al., 1990), apathy (Stöber, 1989; Radostits et al., 2002), depression (Blakley et al., 1982; Steffen et al., 1997; Radostits et al., 2002), kidney and liver damage (Blakley et al., 1982) and death (Blakley et al., 1982; Radostits et al., 2002).

Secondary copper poisoning

Occur mainly two syndromes: chronic copper poisoning by plant and chronic hepatic poisoning.

- Chronic copper poisoning by plants occurs when is ingested small amounts of this mineral and it does not cause significant liver damage. This poisining occurs in sheep grazing Trifolium subterraneum which have low concentrations of copper but increases mineral levels in animal organism causing haemolysis typical of copper poisoning, in addition to liver damage (Radostits et al., 2002).

- Chronic hepatic poisoning by copper occors when animals grazing excessive amounts of Heliotropium europaem and Ecchium plantagineum and can occur excessive retention of this mineral in liver, raising the risk of hemolytic crisis (Radostits et al., 2002).

Diagnosis

Diagnosis of copper poisoning can be performed by dosage of this mineral element in blood, liver, kidney, feces (Undewood and Suttle, 2001; Radostitis, 2007) and activity of e a atividade das enzimas gammaglutamil transferase (GGT) and glutamate dehydrogenase (GLDH) enzymes. The copper concentration considered toxic to animals in theses tissues are described in Table 6.

Differential diagnosis

The diagnosis of copper poisoning should be differentiated of: leptospirosis, postpartum hemoglobinuria, bacilar hemoglobinuria, babesiosis and anaplasmosis (Radostits et al., 2002).

Treatment

The treatment of primary copper poisoning is performed by administration of drugs that act as altidotes such as 3 to 5 g of potassium ferrocianuro diluted in water. Still, use astringent and absorbent drugs as 100 g of magnesium oxide or carbonate, 10 g of tannin (Stöber, 1989). Although administering drugs that increase copper excretion such as: 100 mg of ammonium molybdate and 1 g of anhydrous sodium sulfate diluted in 20 mL of water (McDowell, 1992; Radostits et al., 2002); ammonium tetramolybdate (Radostits et al., 2002; Christodoulopoulos and Roubies, 2007) in the dose of 2.7 mg/Kg of body weight intravenously at intervals of 2 to 3 days between applications or sodium edetate calcium at a dose of 70 mg /Kg of body weight intravenously for two days (Radostits et al., 2002).

The addition of molybdenium and súlfur in diet has been used as a way to prevento r reduce copper poisoning in animals, although this interaction between copper, molybdenum and sulfur is not yet fully understood (Goonerate et al., 1981).

MANGANESE POISONING

Manganese (Mn) is essential for lipid metabolism in animals (Jenkins and Kramer, 1991) and considered as a mineral element with low toxicity to animals (McDowell, 1992; Carvalho et al., 2003), but when in excess it can cause poisoning (McDowell, 1992; Carvalho et al., 2003; Crossgrove and Yokel, 2005).

The maximum tolerable concentration of manganese in diet is high (Jekins and Hidiroglou, 1991), for cattle and

Table 7. Manganese concentration in blood plasma, bile, heart, muscle, kidney and liver of calves fed with different concentrations of manganese (adapted from Jenkins and Hidiroglou, 1991).

Tissues	Concentration of manganese on diet (ppm)			
	40	200	500	1 000
Blood plasma (µg/mL)	0.004^b	0.004^b	0.005^b	0.01^a
Bile (µg/mL)	2.1^c	3.5^c	14.3^b	17.1^a
Heart (µg/g DM)	1.7^{bc}	1.5^c	2.1^{ab}	2.3^a
Muscle (µg/g DM)	2.6	2.5	1.9	1.8
Kidney (µg/g DM)	4.0	3.2	2.9	3.3
Liver (µg/g DM)	7.2^c	10.3^c	15.6^b	26.7^a

[a,b,c] in the same line, averages followed by different letters present significantly difference ($P<0.05$).

Table 8. Toxic dose of manganese in cattle, horse, pig and sheep

Animal specie	Toxic dose of manganese	Effect observed
Cattle	[1]Diets containing 1 000 ppm of Mn	Decrease 22% of body weight gain and 12% feed efficiency
		Increase plasma concentration of cholesterol ester (portion HDL) and triglycerides
		Increase triglyceride concentration in liver
	[2] Diets containing manganese concentration ≥ 2 000 ppm	Poisoning
Horses		
Pigs	[2]Diets containing concentration of 500 ppm of Mn	Poisoning
Sheep	[2]Diets containing concentration ≥ 2 000 ppm of Mn	Poisoning

[1]Jenkins and Kramer (1991); [2]McDowell (1992).

sheep up to 1,000 ppm, for pigs and horses up to 400 ppm.

Table 7 shows that Mn concentrations in plasma, bile, heart and liver of calves fed up to 1,000 ppm of Mn in diet increases significantly. Nevertheless, this increase of Mn concentration in these tissues did not change markedly. In muscle and kidney, Mn concentration was not significantly different. This shows that cattle body is efficient to excrete Mn.

The manganese doses that can cause poisoning in animals are described in Table 8.

The high concentration of Mn in bloodstream also increases triglycerides in liver and reduces sphingomyelin in heart (Jenkins and Kramer, 1991).

Manganese induces autoxidation of dopamine (Archibald and Tyree, 1987; Donaldson et al., 1980; Jimenez Del Rio et al., 1993; Velez-Pardo et al., 1995) with formation of com formação de toxic (semi)quinones, dopamine depletion (Donaldson et al., 1982; Millar and Burttner, 1990; Roy et al., 1994; Takeda, 2003) and the binding of [3H]dopamine (Archibald and Tyree, 1987; Donaldson et al., 1980; Jimenez Del Rio et al., 1993; Velez-Pardo et al., 1995) with the serotonin binding protein (SBP) present in bovine frontal cortex (Jimenez Del Rio et al., 1993; Velez-Pardo et al., 1995) with consequent neurological disorders attributed to the destruction of dopaminergics (Sengtock et al., 1992; Sloot et al., 1994; Velez-Pardo et al., 1995) and reduces the depigmentation of gray matter in the central nervous system (Barbeau, 1984; Velez-Pardo et al., 1995). In addition, the Mn excess also interferes in synaptic neurotransmission because this mineral can enter the nerve endings of motor nerves during the action potential by calcium channel increase the release of neurotransmitters (Drapeau and Nachsen, 1984; Narita et al., 1990; Takeda, 2003).

Animals poisoned by manganese may exhibit the following clinical symptoms: reduced growth and weight gain (Jenkins and Kramer, 1991; McDowell, 1992), anemia, gastrointestinal lesions, (Jenkins and Kramer, 1991) neurological alterations (McDowell, 1992), elevates the plasma concentration of esters and triglycerides colesteral (Jenkins and Kramer, 1991).

The manganese poisoning can be diagnosed through the dosage of this mineral element in liver, manganese concentration above 70 ppm is considered a poisoned animal.

Table 9. Toxic dose of molybdenum for cattle

Animal specie	Molybdenum dose considered toxic	Effect observed
Cattle	[1]Pastures containing 10 mg of Mo/Kg	Poisoning
	[1]Soils containing 10 to 100 mg of Mo/Kg	Poisoning
	[2]Diet containing ≥ 20 mg of Mo/Kg	Poisoning
	[3]5 mg of Mo/Kg of BW during 11 weeks	Reduce LH release
		Reduce conception rate
		Cause anestrus

[1]Radostits et al. (2002); [2]NRC (1996); [3]Haywood et al. (2004).

MOLYBDENUM POISONING

Molybdenum poisoning (Mo) is also known as molybdenosis (Stöber, 1989; Tiffany et al., 2000; Raisbeck et al., 2006) and has been described in New Zealand, Canada, Ireland, Australia and United States (Radostits et al., 2002).

Cattle are more susceptible to Mo poisoning than sheep and horses (Radostits et al., 2002) because bovine digestive tract has a good ability to absorb Mo, while horses have less capacity to absorb this mineral. After absorption, Mo is stored in bonés, liver, kidney and spleen (Stöber, 1989).

In spring, pastures contain a higher concentration of Mo than in autumn, and leguminous plants have a higher capacity of absorption this mineral element than the grasses (Radostits et al., 2002).

Mo poisoning can occur in animals after they ingest foods with high concentration of this mineral and sulfur concentration within normal range (Tiffany et al., 2000) or when food has a high concentration of molybdenum and deficiency of copper (Stöber, 1989).

The concentration of Mo in the diet that is considered safe is ≤ 3 mg/Kg (Radostits et al., 2002), the maximum tolerable in the diet of cattle is 10 mg of Mo/Kg (NRC, 1996) and those that are able to intoxicate animals are described in Table 9. Still, Ainda, Cu:Mo acceptable ratio in diet is 2:1 (Raisbeck et al., 2006), but some authors report that is necessary a ratio of 10:1 (Gooneratne et al., 1989; NRC, 1996).

The Mo sources that cancontaminate the pasture with this mineral are: plants, neutral or alkaline pH and copper deficient soil (Stöber, 1989; Raisbeck et al., 2006); near porcelain factories, paint factory, oil refineries and application of fertilizer containing molybdenum (Stöber, 1989). These pastures contaminated with high doses of Mo can poison animals.

The ingestion of high concentrations of molybdenum in association with sulfur induces the formation of mono, di, tri and tetratiomolybdates in rumen (Wang et al., 1988; Kincaid and White, 1988; Gooneratne et al., 1989; Suttle, 1991; Ward and Spears, 1999; Haywood et al., 2004; Raisbeck et al., 2006). Tetratiomolybdate is not absorbed by digestive tract and binds to copper inhibiting its absorption (Allen and Gawthorne, 1987; Kincaid and White, 1988). The ditiomolybdate and tritiomolybdate can be absorbed and apparently can compete with copper-dependent proteins in liver (Price et al., 1987; Kincaid and White, 1988). The molybdate and tiomolybdate are present in bloodstream increasing copper concentration, thus depletes the reserve of this mineral in liver (Kincaid and White, 1988). There is a reduce in endogenous availability and in copper using by organism of Mo poisoned animals (Wang et al., 1988; Kincaid and White, 1988; Gooneratne et al., 1989; Suttle, 1991; Ward and Spears, 1999; Haywood et al., 2004; Raisbeck et al., 2006) that consequently cause deficiency of copper in theses animals (Kincaid and White, 1988; Ward and Spears, 1999; Bailey et al., 2001; Radostits et al., 2002; Raisbeck et al., 2006). This deficiency of copper occurs more frequently in animals ingesting high concentration of sulfur and/or low concentration of copper in diet (Radostits et al., 2002).

The accumulation of Mo in pituitary causes a disfunction in production and release their hormones which consequently causes reproductive alterations (Phillipo et al., 1986; Haywood et al., 1998) leading to infertility (Haywood et al., 2004).

Cattle poisoned by molybdenum may show symptoms 10 days post excessive ingestion of mineral like: anorexia (NRC, 1996); immunosupression (Raisbeck et al., 2006), persistent diarrhea (Stöber, 1989; NRC, 1996; Radostits et al., 2002; Raisbeck et al., 2006) with foamy liquid feces and undigested food (Stöber, 1989; Raisbeck et al., 2006), dudley hair (specially around the eyes, but also in the rest of the animal's body) opaque hair (NRC, 1996; Stöber, 1989; Radostits et al., 2002), rigidity members and back with altered walking (NRC, 1996; Radostits et al., 2002; Raisbeck et al., 2006). In more severe and serious poisoning, cattle may present reduce in growth and body condition (Stöber, 1989; NRC, 1996; Raisbeck et al., 2006), pale mucose, anemia (Stöber, 1989), leukocytosis (Gengelbach et al., 1997), hindlimb incoordination, more incidence of fractures and reproductive problems (Stöber, 1989) such as

spermatogenesis and libido reduction and severe testicular degeneration (Haywood et al., 1998 e 2004).

Horses poisoned by molybdenum may exhibit the following symptoms: colic by compression, diarrhea and high mortality (Radostits et al., 2002).

The ammonium tetratiomolybdate is used to treat copper poisoning in animals and when is administered in excessive doses can also accumulates in pituitary, brain, adrenal glands, heart and gonads causing Mo poisoning (Haywood et al., 1998).

Sheep poisoned by ammonium tetratiomolybdate may have atrophy or degeneration of adenohypophysis that reduce the production and release of follicle stimulating hormone (FSH) and luteinizing hormone (LH). Therefore, there is ovarian persistent inactivity with presence of degenerated follicles, testicles, ovarian cysts and also testicle inactivity with degeneration of seminiferous tubules which consequently reduces spermatogenesis, reduction of pituitary anterior lobe. Moreover, there is also reduction in production and release of adrenocortical hormone (ACTH) with atrophy of adrenal glands cortex leading to metabolic disorders (Haywood et al., 2004).

The diagnosis of molybdenum poisoning in cattle must be differentiated from paratuberculosis, gastrointestinal parasitism and deficiency of copper (Stöber, 1989).

Animals intoxicated by Mo show have copper concentration in liver below the considered normal (copper concentration in liver considered normal: >65 mg of Cu/Kg of dry liver (Ward and Spears, 1999).

The treatment of molybdenum poisoning is accomplished through administration of 5 mg of copper/Kg of food (Radostits et al., 2002).

SELENIUM POISONING

Selenium (Se) is an essential micromineral to animals (Kommisrud et al., 2005; Haddad and Alves, 2006; Carroll and Forsberg, 2007) and humans. This mineral element is part of several selenoproteins, including glutathione peroxidase (GSH-Px) (Kommisrud et al., 2005; Haddad and Alves, 2006; Paschoal et al., 2006) that acts by removing free radicals, hydrogen peroxides or hydroperoxides and lipoperoxides which are formed during cellular metabolism by converting them into water and oxygen and also as hydroxides of non-toxic fatty acid (Kommisrud et al., 2005; Paschoal et al., 2006; Carroll and Forsberg, 2007), thus protects the cell membrane of oxidative peroxidation (Oliveira et al., 2007) while maintaining the integrity of cells and tissues.
On the other hand, when selenium is ingested on high concentrations above the maximum tolerable dose of selenium in diet (2 ppm) (McDowell, 1992) may cause poisoning in animals and humans, and is also known as selenosis (Stöber, 1989; Carvalho et al., 2003; Papp et al., 2007).

Despite the high number of published studies, the selenium poisoning has not been totally understood, because there are controversies in search results published, fault of dosage of selenium in animal tissue, fault of explicitness on diagnosis and fault of description of clinical signs (Oliveira et al., 2007).

However, when animals ingest high doses of selenium, it can accumulate in organism and the intracellular redox cycle with thiols induces oxidative stress causing damage to cellular components and poisoning by this mineral element in animals and humans (Papp et al., 2007).

The selenium concentration that causes poisoning in animals by this mineral element varies by animal specie and category as shown in Table 10.

A high intake of selenium by animals may be due to several factors, among the most frequent are:

a) The consumption of plants that have high concentrations of selenium. These plants are also known as seleníferas plants and were divided into three groups (Oliveira et al., 2007):

1)   Mandatory accumulating or primary indicator plants: these plants only grow in soils that contain elevated levels of selenium, also called selenífero soil and can contain concentrations ranging from 1 000 to 10 000 ppm of selenium in dry matter. In this group are plants of genera: Astragalus, Stanleya, Oonopsis and Xilorrhiza (Stöber, 1989; Oliveira et al., 2007). The plants convert selenium into a toxic form soluble in water and due to its odor produced by high concentrations of mineral element, the animals avoid consuming these plants (Stöber, 1989).

2)   Secondary accumulating plants: grow in seleníferos or low selenium soils. In this group are: Aster, Atriplex, Castilleja, Comandra, Grayia, Grindelia, Gutierrezia and Machaeranthera. These plants when grow in seleníferos soils present high concentrations of Se in dry matter (Stöber, 1989; Oliveira et al., 2007).

3)   Passive accumulating plants: are the grasses and grains that are destined for feeding animals and humans. These plants can have concentrations ranging from 10 to 30 ppm of selenium in dry matter (Stöber, 1989; Oliveira et al., 2007).

b) The wrong addition of this mineral element in animal food or mineral,

c) Due to soil and pasture contamination by industry wastes with high selenium concentration (Oliveira et al., 2007),

d) Scarcity of rain also predispose animals to selenosis because during dry period does not occur selenium leaching from the soil, so this mineral accumulates in soil which consequently elevates its concentration in soil and plants (Oliveira et al., 2007),

In Brazil, the main cause of selenium poisoning is wrong adding of this mineral in animal diet because the poisoning by seleníferas plants is scarce, due to brazilian soil is highly leached and have low concentration of

Table 10. Toxic dose of selenium for cattle, horse, sheep and pig

Animal specie	Selenium dose considered toxic	Effect observed
Cattle	Food containing ≥ 200 mg of Se/Kg[3,4]	Acute poisoning
	Diet that animal ingest 10 to 20 mg of Se/Kg of BW[2]	Acute poisoning
	Food containing 5 to 40 mg of Se/Kg[1,2]	Chronic poisoning
	Daily supplementation of 6,4 mg of Se/bovine[6,7,8]	Decrease percentage of animals with antibody titer considered considerados protector against rabies, reduce body weight gain and cause muscle lesion (muscle degeneration) with consequent increase of serum creatine kinase (CK)
	Administration of 0,5 mg of Se/Kg of BW[2]	67% of calve mortality
	Administration of 1,2 mg of Se/Kg of BW[4]	Lethal dose
Horses	Daily administration of 0,99 and 1,49 mg of sodium selenium /Kg of BW[5]	Death of animals
	Daily administration of 0,37 mg of sodium selenite/Kg of BW[5]	Subacute to chronic poisoning
	Daily administration of 0,50 mg of sodium selenite/Kg of BW[5]	Acute poisoning
	6 to 8 mg of Se/Kg of BW[4]	Lethal dose
Sheep	Administration of 0,8 mg of Se/Kg of BW[4]	Poisoning
	Administration of 1,6 mg of Se/Kg of BW[4]	Lethal dose
Pigs	1 to 2 mg of Se/Kg of BW[4]	Lethal dose

[1]NRC (1996); [2]NRC (2001); [3]Stober (1989); [4]Radostits et al. (2007); [5]Néspoli et al. (2001), Reis et al. (2008a)[6]; Reis et al. (2008b)[7]; Reis et al. (2009)[8].

organic matter that makes selenium easy to lose, besides the tropical grasses are not good accumulators of selenium, so the concentration of this mineral in brazilian forages is not capable of causing selenosis (Carvalho et al., 2003).

However, in Australia, Canada, Colombia, United States, Ireland, Israel, Mexico and Russia, the occurrence of selenium poisoning in cattle, sheep, horses and swine caused by ingestion of seleníferas plants have been described (Stöber, 1989; Oliveira et al., 2007).

The mechanisms involved in pathogenesis of clinical and pathological selenium poisoning are complex and the descriptions published ser confusing and contradictory (Néspoli et al., 2001). However, the literature describes three classic syndromes of selenium poisoning: one acute and two chronic, Blind Staggers and Alkali Disease (Stöber, 1989; Néspoli et al., 2001; Oliveira et al., 2007).

Acute selenium poisoning

The acute selenium poisoning occurs specially after ingestion of large amounts of seleníferas plants containing high concentration of selenium at once (Stöber, 1989).

The symptoms in cattle with acute selenosis are: high body temperature, pale mucose, mydriasis (Stöber, 1989), blindness, salivation, tachypnea, (Carvalho et al., 2003), spumous and bloody nasal discharge (Stöber, 1989), tachycardia (Carvalho et al., 2003), abdominal colic (Stöber, 1989; Carvalho et al., 2003), dark-colored watery diarrhea, bloating, recumbency, respiratory arrest and death (Stöber, 1989).

Chronic selenium poisoning

Blind staggers occurs after frequent ingestion (several weeks) of seleníferas plants containing moderate selenium concentration as 2 to 3 mg of Se/Kg of body weight/day (Stöber, 1989).

Cattle affected by blind staggers have the following symptoms: drooling, pale mucose, ganshing of teeth, walking in circle, corneal opacity, blindness, generalized muscle paralysis (including muscles of tongue and swallowing), respiratory arrest and death (Stöber, 1989).

Table 11. Selenium concentration considered toxic in blood, serum/plasma, liver, hair and urine of cattle, sheep and pigs

Animal specie	Selenium toxic concentration in tissues				
	Blood (mg/L)	Serum/Plasma (mg/L)	Liver (ppm)	Hair (ppm)	Urine (ppm)
Cattle	2.0-2.4[1]	2.5-3.5[1]	0.75-1.25[1]	≥ 5[1,2]	≥ 4[2]
Sheep	0.2-0.3[1]	2.0-3.0[1]	10-15[1]	4.0-6.0[1]	
Pigs	2.0-3.0[1]		1.5-3.0[1]	4.0-6.0[1]	

Underwood and Suttle (2001d)[1]; Radostits (2007)[2].

Table 12. Manganese concentration in plasma, bile, heart, muscle, kidney and liver of calves fed with different concentrations of zinc (adapted from Jenkins and Hidiroglou, 1991).

Tissues	Zinc concentration in diet (ppm)				
	40	200	500	700	1 000
Plasma (µg/mL)	1.5[c]	2.5[c]	5.6[b]	6.1[b]	16.6[a]
Bile (µg/mL)	1.0[c]	1.2[c]	3.1[b]	3.0[b]	6.4[a]
Heart (µg/g DM)	74.4[d]	79.5[cd]	90.5[bc]	98.4[b]	136.1[a]
Muscle (µg/g DM)	59.3[c]	62.3[bc]	71.8[bc]	82.2[ab]	94.4[a]
Kidney (µg/g DM)	138[c]	634[d]	1 210[c]	1 779[b]	2 498[a]
Liver (µg/g DM)	677[d]	1 625[c]	3 138[b]	3 821[a]	3 647[a]

[a,b,c,d] in the same line, averages followed by different letters present significantly difference (P<0,05).

Alkali disease occurs after long ingestion of grasses and cereals containing moderate concentrations of selenium bound to proteins (Stöber, 1989).

Cattle affected by alkali disease exhibit the following symptoms: poor appetite, staggering gait, anemia (Stöber, 1989), rough and dull hair (Carvalho et al., 2003), alopecia usually at the tip of tail (Stöber, 1989; Carvalho et al., 2003), deformation of shells (Rosenberger, 1989; Carvalho et al., 2003), laminitis (Carvalho et al., 2003), claudication (Stöber, 1989; Carvalho et al., 2003) and ataxia (Stöber, 1989).

Calves born from cows affected by alkali disease usually have deformed shells and also be poisoned by consuming high-selenium milk.

Diagnosis

Diagnosis of selenium can be accomplished through determination of this mineral in blood, urine and milk (Radostitts, 2007). The selenium concentration considered toxic in tissues is described in Table 11.

Differential diagnosis

Acute selenium poisoning: arsenic poisoning, blind staggers, lead poisoning, vitamin A deficiency, botulism, central nervous system disorder.

Alkali disease: Osteomalacia, ergotism, fescue foot (lameness by fescue) (Stöber, 1989).

ZINC POISONING

Zinc (Zn) poisoning in cattle, sheep and pigs probably occurs less frequently due to these species tolerate high doses of this mineral in diet (McDowell, 1992; NRC, 1996; Radostits et al., 2002). According to Stöber (1989), the daily intake of food conteiing 2,000 ppm of Zn for six weeks only increased the blood concentration of zinc and cows ingesting daily doses of 8 grams of Zn, the only change observed was this mineral increase in milk. Also, calves that ingested food containing up to 1,000 ppm of Zn was not observed poisoning signs by this mineral element.

Table 12 shows concentration of Zn increased significantly in plasma, bile, heart, muscle, kidney and liver of calves feeding up to 1,000 ppm of Zn.

The dose of zinc that can poison animals is not yet totally defined, but that was already determined is described in Table 13 (Radostits et al., 2002).

The high intake of zinc by animals may be due to several factors, among the most frequent are: addition of excessive amounts of zinc in animals food (Stöber, 1989; Radostits et al., 2002), pastures contaminated with

Table 13. Zinc toxic dose for cattle, sheep and pigs

Animal Specie	Zinc toxic dose	Effect observed
Cattle	700 mg of Zn/Kg of diet[1,4]	Calves presented reduce in body weight gain, food intake, nitrogen digestibility and hematocrit
	706 mg of Zn in milk[6]	High percentage of calves showing pneumonia, urinary disorders, diarrhea and death
	900 to 1 000 of Zn/Kg of diet[1,2,4]	Decrease in growth, nitrogen digestibility and hematocrit
	2 000 mg/Kg of diet[3]	Decrease in milk production
	75 g of zinc oxide during 3 to 4 days[2]	Probably is toxic for adult cattle
	150 g of zinc oxide[2]	Cattle death
Sheep	1 000 mg of Zn/Kg of diet[3,5]	Reduction in feed efficiency and body weight gain
	1 500 mg of Zn/Kg of diet[3]	Reduction in food intake
	1 700 mg of Zn/Kg of diet[3]	Caused a perversion of appetite
Pigs	4 000 mg of Zn/Kg of diet[3]	Reduce growth

[1]NRC (1996); [2]Stöber (1989); [3]McDowell (1992); [4]Jenkins and Hidiroglou (1991); [5]Ott et al. (1966); [6]Graham et al. (1987; 1988).

Table 14. Concentration of zinc found in liver and kidney of cattle poisoned by this mineral element (Adapted from Wentink et al., 1985).

Animal specie	Concentration of zinc	
	Liver (ppm)	Kidney (ppm)
Cattle	420 to 1 600	910 to 1 680

smoke from galvanizing factures (Stöber, 1989; Radostits et al., 2002), places painted with high-zinc paints where animals can lick them (Stöber, 1989; Radostits et al., 2002) and food transport in galvanized containers (Stöber, 1989).

Cattle poisoned by Zn may exhibit the following symptoms: inappetence (Allen et al., 1983), drowsiness, somnolence, paresis (Radostits et al., 2002), chronic constipation (Stöber, 1989; Radostits et al., 2002), colic (Stöber, 1989), green-colored diarrhea and sometimes bloody diarrhea (Stöber, 1989; Radostits et al., 2002), dehydration, subcutaneous edema, anemia (Allen et al., 1983), marked reduction in milk production (Stöber, 1989; Radostits et al., 2002), reduction in growth of calves, heart failure (Stöber, 1989) and decrease of cellulolytic bacteria probably due to a reduction on use of cellulose by these bacterias with an inhibitory effect on the cellulolytic enzymes produced by them (Eryavuz and Dehority, 2009).

Horses poisoned by zinc may exhibit the following symptoms: weight loss, degenerative arthritis specially in fetlock joint, osteoporosis and claudication (Radostits et al., 2002).

Acute poisoned pigs may show the following symptoms: anorexia, arthritis, bleeding in armpits, gastritis and enteritis, and in case of chronic poisoning may show: anorexia, lethargy, rough hair, claudication,

subcutaneous hematoma and recumbency (Radostits et al., 2002).

The confirmation of the diagnosis of zinc poisoning is done when it is detected high concentrations of this mineral in tissues and body fluids as presented in Table 14.

Diagnosis has to be differentiated to rickets and acute arthritis (Radostits et al., 2002).

The treatment of zinc poisoning includes administration of iron hydroxide as an antidote. Still, astringent and absorbent drugs as 100 g of magnesium oxide or carbonate and 10 g of tannin may be used (Stöber, 1989).

CONCLUSION

The toxic doses has not been known yet because there is disagreement between results of published studies, and still the physiological mechanisms involved on mineral poisoning are also not yet understood. For some mineral elements, the published papers that have evaluated these mechanisms are lacking probably due to the difficulty of describing the physiological mechanisms, changes involved in the process of poisoning and also difficulty of establishing toxic dose of a mineral element due to the dependence of each mineral element, its form,

specie and age of animals and the interaction between minerals in metabolism.

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