

Overview Appendix 7: Cadmium exposure in cattle: a review

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Abstract

No biological role has been described for cadmium (Cd) in animals and its presence in animal tissue is considered unnecessary. Cadmium is considered to be one of the most toxic substances in the environment due to its wide range of organ toxicity and long elimination half-life. Batteries are an important source of Cd pollution, additionally, combustion of coal, smelting, mining, alloy processing and industries that employ Cd as a dye are also potential sources of Cd pollution. Agricultural practices such as the application of sewage sludge and contaminated fertilizers are also sources of Cd contamination. Absorption of Cd occurs via the respiratory and digestive system. Approximately 10 to 50% of Cd fumes are absorbed by the respiratory system. While, Cd is poorly absorbed via the digestive tract, compared to similar divalent cations, Zn and Fe; approximately 5 % of oral Cd is absorbed. Once absorbed, Cd circulates in red blood cells or bound to albumin in plasma. Cadmium interacts with the metabolism of essential minerals; calcium, zinc, iron, copper and selenium. The majority of newborn ruminants have a low Cd burden. Accumulation occurs slowly over time, primarily in liver and kidneys. In the liver it may induce and bind metallothionein, this complex is released slowly into circulation and then accumulates in kidneys. At high levels dietary Cd can cause decreased feed intake, and lowered weight gain, anaemia, decreased bone absorption and abortions and Cd toxicity has been reported in many species including cattle. This paper reviews the literature pertaining to Cd exposure and its effects in cattle.

Introduction

Cadmium (Cd) has no known biological function in either animals or humans but mimics the actions of other divalent metals that are essential to diverse biological functions (EFSA, 2009). Bioavailability, retention and consequently toxicity of Cd are affected by several factors such as nutritional status (low body iron (Fe) stores) and multiple pregnancies, pre-existing health conditions or diseases (EFSA, 2009). Cadmium has the ability to cross various biological membranes by different mechanisms (e.g. metal transporters) and when inside bind to ligands with exceptional affinity (e.g. metallothioneins).

Batteries are the main source of Cd pollution, however processes like combustion of coal and mineral oil, smelting, mining, alloy processing and industries that use Cd as a dye (Cd sulphide: yellow; Cd selenite: red) in their manufacturing processes are also potential sources of Cd pollution (Swarup *et al.*, 2007). Cadmium is presently listed as number 7 of 275 of the most hazardous substances in the environment, behind arsenic, lead, mercury, vinyl chloride, polychlorinated biphenyls and benzene by the Agency for Toxic Substances and Diseases Registry (ATSDR; Agency for Toxic Substances and Diseases Registry, 2007). This listing takes the toxicity of the substance and the likelihood of exposure at a US National Priority Cleanup Sites into account. A review conducted by Patrick (2003) suggests that Cd is considered to be one of the most toxic substances in the environment due to its wide range of organ toxicity and long elimination half-life. Similar to humans, Cd accumulates slowly in animal tissues over time, primarily in liver and kidneys. At very high levels dietary Cd can cause decreased feed intake, and lowered weight gain, anaemia, decreased bone absorption and abortions (NRC, 1980). Sewage sludge and contaminated fertilizers are considered important sources of Cd contamination in the USA (Patrick, 2003). Cadmium as a pollutant in phosphate fertilisers (Järup, 2003), is added to land through normal farming practice (Roberts *et al.*, 1994; Martelli *et al.*, 2006). Whilst Cd levels in fertilisers sold in the European Union are not directly covered by the EU Fertiliser directive 76/116/EEC, this is under revision. Where the long term addition of phosphate fertiliser (30kg P/ha/annum for 31 years) has been examined under Irish conditions, a 0.07 mg/kg rise in soil Cd levels occurred; soil Cd levels rose from 0.23 to 0.30 mg/kg in the top 10cm of the soil (DAF, 2000). Soil Cd levels of 1 mg/kg are regarded as polluted soils (Fay *et al.*, 2007). Work conducted by Telford *et al.* (1982) describes an 11-fold and 6-fold increase in liver and kidney Cd concentrations, respectively in sheep fed sludge-grown corn silage compared with controls after 255 days exposure. Air concentrations of Cd of between 0.01 and 0.35 µg/m³ have been reported (US Department of Health, Education and Welfare, 1966), with the highest

concentrations been demonstrated in industrialised cities. Cadmium toxicity has been reported in many species including cattle (Powell *et al.*, 1964; Lynch *et al.*, 1976). The majority of newborn ruminants have a low Cd burden, but progressive accumulation occurs with time primarily in kidney and liver (Underwood, 1977; Langlands *et al.*, 1988). Cadmium is a known human carcinogen (reviewed by Filipic *et al.*, 2006); however, such affects in animals has not been described therefore will not be discussed in this paper.

The aim of this paper is to review the literature pertaining to Cd exposure and its effect in cattle.

Dynamics of Cd absorption

The respiratory and digestive systems have both been implicated in Cd absorption, but intestinal absorption is relatively low compared to similar divalent cations, zinc (Zn) and Fe. Approximately 10 to 50 % of Cd fumes are absorbed by the respiratory system, whilst Cd is poorly absorbed via the digestive tract; approximately 5 % of oral Cd is absorbed. Cadmium interacts with the metabolism of essential minerals; calcium (Ca), Zn and Fe (Goyer, 1995; Peraza *et al.*, 1998) and copper (Cu; Peraza *et al.*, 1998). Intestinal absorption is influenced by the type of diet and nutritional status of the animal involved (WHO, 1992), with Fe status being of particular importance. Iron deficiency increases the gastrointestinal absorption of Cd (Goyer, 1995) in piglets (Öhrvik *et al.*, 2007), but the precise mechanism of the increased intestinal Cd absorption has not been elucidated. In women low blood ferritin concentrations were associated with raised blood Cd concentrations (Berglund *et al.*, 1994); indeed Fe deficiency increases the gastrointestinal Cd absorption rate from 5 to 20 % (Nordberg *et al.*, 1985). More recent work conducted by Reeves and Chaney (2001; 2002; 2004) suggests that even marginal dietary deficiencies of Fe, Zn and Ca increase the bioavailability of Cd. Once absorbed, Cd circulates in red blood cells or bound to albumin in plasma. In the liver it may induce and bind MT, this complex is released slowly into circulation and then accumulates in kidneys. It may also be stored in bone, pancreas, adrenals and in the placenta, however, liver and kidney account for half of the bodies total stores (Pope and Rall, 1995).

As a non-essential element Cd is unlikely to enter the body by a Cd specific transport mechanism, and many studies have suggested that Cd crosses various membranes utilising other elements transport mechanisms (Martelli *et al.*, 2006). After inhalation Cd accumulates in the olfactory bulb (Sunderman, 2001), and in the lungs where unlike other heavy metals it can pass through alveolar cells and enter the blood stream (Bressler *et al.*, 2004). The exact

mechanism(s) by which Cd enters circulation has yet to be fully elucidated, it may be bound to chelators such as glutathione or cysteine, or Cd most likely uses transporters/channels dedicated to other ions and biomolecules.

The low molecular weight metal binding protein MT is a small cystine-rich protein involved in the binding, transport and detoxification of excessive Cd (and other heavy metals; WHO, 1992; Öhrvik *et al.*, 2007). It was proposed that intestinal Cd absorption may be limited by the MT, which is synthesised in the intestinal epithelium following oral Cd exposure (Min *et al.*, 1992), however Klaassen *et al.*, (2009) reports that MT plays a minimal role in the gastrointestinal absorption of Cd and is more important in Cd retention by tissues. Some studies suggest that divalent metal transporter 1 (also DCT1, Nramp2 or SLC11A2; transporter responsible for the absorption of non-haeme iron; Tallkvist *et al.*, 2001) localised in the brush boarder of the human (Griffiths *et al.*, 2000, Martelli *et al.*, 2006) and rat (Trinder *et al.*, 2000; Park *et al.*, 2002) duodenum and also ferroportin 1 (FPN1) in the pig (Öhrvik *et al.*, 2007) may also act as a Cd intestinal transporter. Gene expression of DMT1 is up-regulated in subjects with Fe deficiency (Han *et al.*, 1999). Studies of microcytic anemic *mk/mk* mice (Suzuki *et al.*, 2008) and Fe deficient piglets (Öhrvik *et al.*, 2007) show increased expression of DMT1, but similar Cd concentrations to non deficient animals, suggesting that another functional transporter(s) may also be involved in intestinal Cd transport. In rats fed a and Fe deficient diet, DMT1 mRNA was also increased, however, in this study there was an increased absorption of Cd from the gastrointestinal tract (Park *et al.*, 2002).

The acidic environment of the digestive tract favours Cd transport by the broad specificity proton-metal co-transporter DMTI at the apical membrane of enterocytes (intestinal absorptive cells). Most Cd ingested is bound to MT and phytochelatin (small cystine rich peptides capable of binding metal ions including Cd, and are assumed to be involved in the accumulation, detoxification and metabolism of metal ions in plant cells; Grill *et al.*, 1987). The Cd/MT conjugate is most likely degraded by the gastric juices, releasing Cd and making it available for transport by DMT1 (Bressler *et al.*, 2004). Duodenal enterocytes express an iron responsive element (IRE) containing a splicing variant of DMTI that is targeted to the plasma membrane, and whose translation is enhanced by Fe regulatory protein (IRP) binding. Translation of DMT1 is up-regulated under Fe-poor conditions to allow for more Fe absorption (Bressler *et al.*, 2004), therefore Cd uptake by ingestion intimately depends on the iron status of the animal (Martelli *et al.*, 2006). Uptake of Cd may also be mediated by other transport proteins such as metal transport protein 1, calcium channel proteins, and the 8-

transmembrane zinc related iron protein (ZIP8) to reach target tissues (Klaassen *et al.*, 2009). Ferroportin, the Fe transporter at the basolateral membrane is believed to be involved in Cd export into the blood stream, but calcium-ATPases and Zn exporters, may also contribute to Cd export from enterocytes (Martelli *et al.*, 2006).

Inside cells Cd meets ligands of exceptionally high affinity, MTs, the major zinc-binding proteins. Metallothionein functions in Cd detoxification primarily through high affinity binding of Cd to MT and in the kidneys and liver MT concentrations are high (Klaassen *et al.*, 2009). The rate of excretion of Cd is slower than that of uptake; hence the need to detoxify and store Cd by an immobilization mechanism is a consequence of this slower rate of elimination (George and Coombs, 1977, Klaassen *et al.*, 2009). Along with glucocorticoids, the essential metals Zn (Min *et al.*, 1991, 1992) and Cu, and the toxic metal mercury, intracellular Cd induces metallothionein synthesis in many organs including the liver and kidneys. Molecules other than MT, such as albumin, cystine, glutathione and sulfhydryl-rich proteins can also form associations with Cd. Metallothionein expression however was not affected by Fe status in piglets (Öhrvik *et al.*, 2007). Induction of metallothionein synthesis by Zn (Min *et al.*, 1991, 1992) ensures sufficient MT to bind and detoxify ingested Cd. *In vitro* studies in rats show that intestinal Zn-MT incubated with Cd chelated with cysteine (Cd-Cys), the Cd dissociates from the cysteine and exchanges with the Zn bound the MT, thus allowing the MT to act as a detoxifier and transporter.

Cadmium toxicity

Studies of Cd toxicity in animal cells have unveiled a vast set of cellular targets for the deleterious action of this metal and most pathological signs of Cd intoxication arise from specifically damaged organs. Two organs are implicated in the development of Cd toxicity, namely the kidneys and bone (Goyer, 1995). Proximal tubular dysfunction develops in the kidneys, resulting in a decreased absorption of amino acids, glucose, Ca, phosphate, and low molecular weight proteins. In humans damage to the proximal renal tubules occurs when the concentration of Cd reaches approximately 200 µg/g; the resultant losses of bone minerals in the urine can lead to significant bone mineral depletion and fractures (reviewed by Spivey Fox, 1987). The most severe form of the disease was observed in Japan, Itai-itai disease, in women, following 20 years exposure to Cd in food and drinking water. Human exposure to Cd, as a result of smoking, increases renal Cd concentrations from a mean of 20 to 40 µg/kg (Elinder *et al.*, 1983) and blood concentrations from a mean of 0.87 µg/l to 1.12 µg/l (Palminger Hallen *et al.*, 1995). Studies in cattle suggest that females accumulate increased

Cd in kidneys compared with males (Lopez-Alonso *et al.*, 2000). The form of Cd administered may affect the degree of nephrotoxicity. A single injection of Cd bound to MT at doses as low as 0.2 mg/kg was nephrotoxic in mice, whereas administration of Cd chloride up to 3 mg/kg did not affect renal function (Dorian *et al.*, 1995). Indeed, in rats dietary Zn and Se seem to exert a cooperative effect in protection of Cd induced hepatic damage, but not renal damage (El Heni *et al.*, 2008). The authors explained the difference in affect between the two forms due to the lower concentration of Cd in target cells (convoluted tubules) following administration with Cd chloride compared with following Cd bound to MT. Cadmium has also been implicated in the development of bone pathology. Deposition of Cd in bone may interfere with processes of calcification, decalcification and bone remodelling (Goyer, 1995). The kidneys synthesise the erythropoiesis regulating hormone, erythropoietin, and it transforms monohydroxylated vitamin D into dihydroxy derivatives which play a prominent role in bone formation and resorption. The presence of Cd in the kidneys may decrease erythropoietin (Horiguchi *et al.*, 2000) and dihydroxy vitamin D production (Brzóska and Moniuszko-Jakoniuk, 2005) and as such affect bone morphology. Within the bone, Cd bone concentrations have been reported to be increased by a factor of 50 in the last 600 years, with the majority of that effect believed to be in the past 100 (Ericson *et al.*, 1991). Toxicity of Cd in humans has been characterised by multiple fractures, bone pain, osteoporosis and osteomalacia in conjunction with renal disease (Noda and Kitagawa, 1990). However, there are other mechanisms by which Cd toxicity develops. Cadmium displays a high affinity to glutathione to which it may bind, this complex is excreted in bile. Cadmium decreases the activity of many antioxidant enzymes. Selenium or zinc may be substituted by Cd in metalloenzymes; and lowered concentrations of selenium and glutathione peroxidase have been reported in Cd-exposed workers (Wasowicz *et al.*, 2001). Furthermore, work conducted in The Netherlands demonstrates that exposure to low levels of Cd impairs reproduction in dairy cows (Kreis *et al.*, 1993). Interestingly, despite the suggestion that Cd absorption increases during pregnancy, Cd bound MT does not cross the placenta, ensuring that the newborn is born with a low Cd burden, however, the transportation of Zn and Cu are not affected (Goyer and Cherian, 1992). The ability of Cd to cross the placenta is dependent on Zn and Cu status of the dam. Cd-exposed rats given sufficient amounts of Zn and Cu have Cd free progeny compared with those fed a zinc and copper deficient diet (Goyer and Cherian, 1992).

Blood Cd concentrations in animals

Lui (2003) describes the concurrent poisoning of lead (Pb) and Cd in sheep and horses near a non-ferrous metal smelter in China. Affected horses mean blood Cd concentrations were 170 µg/l compared with control horses blood concentrations of 30 µg/kg. While mean blood Cd concentrations in the affected sheep were 370 µg/kg compared with 20 µg/kg in control animals. Work conducted in the mid seventies in the USA reported Cd concentrations in a number of different domestic species including swine, cattle, dogs and horses in the Midwestern region. Blood Cd concentrations were at or near the detection limit for their assay of 0.005 ppm, equivalent to 5 µg/kg. Research conducted in an industrialised area of North West Spain, Galicia reported blood concentrations of Cd in six to ten month old calves and cows (Lopez Alonso *et al.*, 2000). The mean blood Cd concentration was 0.373 and 0.449 µg/l in calves and cows, respectively. Another study conducted by the same laboratory, focused on the industrial area of Asturias in Northern Spain, reported similar blood Cd concentrations in ten month old cattle of 0.403 µg/l (ranging from non detectable to 1.91 µg/l) compared with Cd concentrations of 0.402 µg/l (ranging from non detectable to 2.25 µg/l) in similar aged calves in a non industrial area. Despite the similar blood concentrations, kidney, liver and muscle concentrations were higher in the calves located in the industrial area compared with those located in a rural area; suggestive that although exposed to higher Cd, this is not always associated with raised blood concentrations. This Spanish study concludes that trace element status of the calves was affected, with almost half the calves in the industrialised zone demonstrated to have lowered tissue Cu concentrations, underlying the importance of heavy metals effects on trace element status. Compared to these Spanish studies, research conducted in India, report substantially higher concentrations of blood Cd, using similar methodologies. Patra *et al.* (2005) determined blood and milk Cd concentrations in 210 lactating cows reared and kept within 2 km radius of a number of different industrial units or in a non-polluted area to serve as controls. Their results are suggestive that cows reared and kept near a steel manufacturing plant had higher blood Cd concentrations (mean 232 µg/l; ranging from 90 to 410 µg/l) compared with cows kept near other industrial sites or in a non polluted area (mean 28 µg/l; ranging from 0 to 50 µg/l). Interestingly, further research by the same group suggests that whole blood Fe was lower in the cows near the steel processing plant compared with those in the non-polluted areas (Patra *et al.*, 2006). Additional sampling of cows in the different industrial areas revealed mean Cd concentrations of 25 µg/l (ranging from non detectable to 50 µg/l) were reported in cows in unpolluted areas (n = 30), and highest Cd concentrations near the steel processing plant (n = 46); mean Cd

concentrations 127 µg/l (ranging from non detectable to 410 µg/l) were reported in similar aged cows (Patra *et al.*, 2007). While work conducted by the same Indian laboratory reported similar blood Cd concentrations in another study (Swarup *et al.*, 2007).

Some studies have examined the ability of supplemented Cd to raise blood Cd concentrations. Work conducted by Lynch *et al.* (1976) determined that 15 mg Cd given daily to male Holstein calves increased mean blood Cd concentrations, estimated by atomic absorption spectrophotometer, to $21 \pm \text{SD } 0.85$ µg/l compared with $10 \pm \text{SD } 0.46$ µg/l in control calves. More recent work examined the effect of dosing with water containing a Cd chloride solution at a dose rate of 0.06 mg Cd/kg (approximately 18 mg per animal) to 300 kg male *Bos indicus* cattle (Foihirun *et al.*, 2006). Concentrations of Cd increased from 0.25 µg/l to 3.62 µg/l after dosing, values peaked 30 to 60 minutes after feeding and by 240 minutes Cd concentrations had returned to baseline. The authors speculated that the speed of the increase may have been related to the bioavailability of the Cd chloride given in a solution of water. A study conducted on sheep suggests that the increase in Cd concentrations in blood following administration is variable (Houpert *et al.*, 1995; 1997). Mean Cd concentrations 450 to 5800 µg/l depending on dose administered was achieved in the 1995 study. Houpert *et al.*, 1997 reported that oral administration of Cd chloride (25 mg/kg, enclosed in gelatin capsules) resulted in a range of blood concentrations (2.5 to 80 µg/l) one to two days after dosing, with concentrations declining slowly until 21 days after treatment. While the same study demonstrated that the administration of an intravenous Cd bolus, at a dose rate of 0.1 mg/kg, raised blood Cd concentrations to between 350 to 950 µg/l. This decreased rapidly within hours and then more slowly in the following days. In mice treated with a single oral dose of Cd (200 µg), blood Cd levels did not peak till 104 h after treatment (Wilson and Bhattacharyya, 1997), compared with mice treated with only 3 µg where the total amount of Cd in the blood decreased from 1.9% of the absorbed dose at 30 minutes to 0.3% of the absorbed dose by 72 hours (Jonah and Bhattacharyya, 1989). It was believed that the amount of Cd associated with metallothionein and other Cd-binding proteins in intestinal cells was higher at the higher oral dose, thus providing a pool for release into the blood that was not immediately cleared by the liver and kidneys.

Cadmium concentrations in animal tissues

Regulatory limits of maximum Cd levels in muscle, liver and kidneys of cattle for human consumption within the European Union are set by the Commission Regulation No. 1881/2006 (amended by No. 629/2008) at 0.05, 0.5 and 1.0 mg/kg wet weight, respectively.

Many studies worldwide have reported the concentrations of Cd in meat, liver and kidneys of meat producing animals. A study conducted in the mid seventies in the USA revealed a median Cd concentration in livers and kidneys of sampled cattle, swine and dogs was 0.2 and 0.6 mg/kg, respectively (Penumarthy *et al.*, 1980). Interestingly, this US study suggests that Cd concentrations were higher in equine livers (20 times) and kidneys (4 times) compared with other species sampled. A number of studies were conducted in Spain. Miranda *et al.* (2001) examined the Cd concentrations in liver, kidneys and meat in calves in the Asturias region of Northern Spain, an industrial area in a region that contains a large mining area. This study collected slaughterhouse samples from 6 to 12 month old calves (n = 312). Mean Cd concentrations were 0.031 mg/kg (range 0.003 to 0.221 mg/kg) in liver samples, and 0.161 mg/kg (range 0.004 to 0.717 mg/kg) in kidneys. Pig slurry application to agricultural land has been implicated as a possible source of heavy metal contamination for food production. Kidney and liver concentrations were determined in 195 calves following slaughter for meat production in the Deza region of Spain, an area noted for its pig production, and hence its high level of pig slurry application to grazing areas (Blanco-Penedo *et al.*, 2006). Mean Cd concentrations were 0.014 (range ND – 0.086) mg/kg in liver and 0.072 (range ND – 0.328) mg/kg in kidneys. These concentrations were similar to other studies conducted in non-polluted area of Spain (liver concentrations, 0.032 mg/kg; kidney concentrations, 0.071 mg/kg; Lopez Alonso (1999). More recent work conducted by the same laboratory suggests that samples obtained from calves in industrialised areas have higher concentrations of liver and kidney concentrations of Cd (Cd: liver 0.030 kidney 0.161 mg/kg) compared with those in calves from rural areas (Cd: liver 0.023, kidney 0.096 mg/kg; Miranda *et al.*, 2005). Jamaica is an island known for its Cd enriched soils (Lalor, 1998) in 2009 Nriagu *et al.* reported higher concentrations of Cd in bovine livers (geometric mean 0.378 mg/kg) and kidneys (geometric mean 1.48 mg/kg) compared with other studies. Age was highly associated with kidney Cd concentrations and older cows had much higher concentrations of Cd compared with younger animals.

Exogenous Cd increases Cd concentrations in both liver and kidneys in rats (Bebe *et al.*, 1996) and sheep (Rogowska *et al.*, 2008). In a study conducted in Poland, sheep were slaughtered 1, 12, 48 or 96 days after receiving 10 mg/kg Cd body weight (total dose 550 mg per sheep) and Cd concentrations determined in a number of tissues including liver and kidney. An untreated control group was slaughtered to determine basal Cd concentrations prior to the start of the experiment. Kidney and liver Cd concentrations were higher in the

animals with time. A detoxification preparation, Monk-1, given to half of the animals in this study, decreased Cd concentrations in the kidneys, liver, muscle, and duodenum. Oral Cd fed to weanling rats at a rate of 5 mg/l in drinking water for a period of 4 weeks increased liver Cd concentrations to approximately 35 mg/kg and kidney concentrations to approximately 60 mg/kg (Bebe *et al.*, 1996). Interestingly, Cd was not measurable in either plasma or erythrocytes in this study.

Data from literature on the levels on Cd in livers and kidneys of cattle from various countries are presented in Table 1. Average concentrations (range) in mg/kg wet weight are given.

Table 1: Data from recent literature on the concentration of Cd in livers and kidneys of cattle from various countries. Average concentrations (range) are given in mg/kg wet weight.

Country	Animal	Age	Liver Cd	Kidney Cd (*cortex only)	Reference
<i>EU Member States</i>					
Poland	Bison (Free ranging)	1yr	0.09±0.01 (0.07-0.10)	0.21±0.03 (0.18-0.25)* ¹	Wlostowski <i>et al.</i> , 2006
		2yr	0.22±0.1 (0.10-0.35)	0.41±0.07 (0.35-0.50) * ¹	
		4yr-6yr	0.43±0.03 (0.40-0.48)	1.24±0.38 (0.86-1.82) * ¹	
		7yr-12yr	0.45±0.08 (0.31-0.58)	2.79±0.66 (1.95-3.52)* ¹	
	Domestic cattle	8yr-12yr	0.2±0.06 (0.09-0.27)	1.30±0.47 (0.68-2.0) * ¹	
Poland	Cattle	<2yrs	0.159±0.098 (0.06-0.487)	0.425±0.195 (0.104-0.937)	Zasadowski <i>et al.</i> , 1999
		>2yrs	0.263±0.166 (0.081-0.672)	1.703±1.106 (0.59-4.275)	
Poland	Cattle		0.12	0.61	Falandysz, 1993
NW Spain	Cows	3yr-16yr	0.0547 (0.013-0.564) * ⁴	0.320 (0.0298-3.393) * ⁴	López-Alonso <i>et al.</i> , 2004
NW Spain	Calves	6mth-10mths	0.00756-0.00798 (ND-7.99)	0.0513-0.0579 (0.00243-1.302)	López-Alonso <i>et al.</i> , 2000
	Cows	2yr-16yr	0.0833 (0.0234-0.246)	0.388 (0.110-1.346)	
Spain	Cattle	6mths-12mths	0.0307±0.00124	0.161±0.00703	Miranda <i>et al.</i> , 2001
N Spain	Cattle	9mth-12mth	0.0229 (0.00643-0.221) Rural	0.0964 (0.0042-0.545) Rural	Miranda <i>et al.</i> , 2005
			0.0296 (0.00339-0.131) Industrial	0.161 (0.0235-0.717) Industrial	
Sweeden	Cattle		0.07	0.39	Jorhem <i>et al.</i> , 1991
Finland	Cattle		0.061	0.35	Niemi <i>et al.</i> , 1991
Finland	Cattle	Heifers	0.036		Tahvonen and Kumpulainen, 1994
		Cows	0.066		
Slovenia	Cattle		0.094	0.373	Doganoc, 1996
Netherlands	Cattle	3mths-13yr	0.16 Control area* ²	1.61 Control area* ³	Spierenburg <i>et al.</i> , 1988
			0.35 Polluted area* ²	3.96 Polluted area* ³	
<i>Non-EU countries</i>					
Australia	Cattle		0.04-0.21	0.1-0.66	Langlands <i>et al.</i> , 1988
Jamaica	Cattle		3.24 (ND-82.1)	7.92 (0.012-117)	Nriagu <i>et al.</i> , 2009

Kazakhstan	Cattle		0.05-0.79	0.13-1.06	Farmer and Farmer, 2000
Iran	Cattle	1yr-10yr	0.0497	0.1371	Rahimi and Rokni, 2008
Morocco	Cattle		1.45 (0.82-2.02) * ²	4.26 (2.36-5.58) * ³	Sedki <i>et al.</i> , 2003
New Zealand	Cattle	Heifers	n/a* ²	<0.04-0.82* ³	Roberts <i>et al.</i> , 1994
		Beef cows	n/a* ²	<0.04-2.06* ³	
		Dairy cows	n/a* ²	<0.04-1.65* ³	
China	Cattle	2yr - 4yr	<0.5, 1.31, 2.47	2.15, 6.64, 38.3	Cai <i>et al.</i> , 2009

*¹ Kidney cortex only

*² Results converted from dry weight to wet weight by dividing by 3.52, based on the assumption that the water content of a liver is 77.9 %

*³ Results converted from dry weight to wet weight by dividing by 3.52, based on the assumption that the water content of a kidney is 70.2 %

*⁴ Geometric means are presented

Interaction between Cd and essential trace elements

It is believed that a better understanding of the interaction of Cd with other elements may provide the key to understanding the effects of Cd on health. 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 (EFSA, 2009), resulting in older animals having higher liver and kidney Cd concentrations (Nriagu *et al.*, 2009) even if the levels in their diets and water are consistently low (NRC, 2005). Perturbation of Ca, Zn or Fe homeostasis plays a key role in Cd toxicological action that involves a general threat to basic cellular functions (Goyer, 1995, Martelli *et al.*, 2006).

A review conducted by Bremner (1979) outlines the traditional approach to studies on heavy metal toxicity; determination of dose response relationships, characterisation of the metals accumulation in the body and the display of classical signs of toxicosis. However, Bremner cautions against this simplified approach and highlights the importance of examining the earlier toxic affects of heavy metals, especially the disturbance in the metabolism of essential trace elements in the animal. Bremner and Campbell (1978) state that the toxicity of heavy metals cannot be considered without due regard being given to dietary composition and the nutrition status of the animal. Cadmium interacts with a number of different trace elements including Ca, Cu, Fe, Zn, proteins, and vitamins C and D (NRC, 1980). The interaction between Ca and Cd is well defined in humans by the development of Itai-itai disease in Japanese women, a disease associated with the development of bone deformities, osteomalacia and an increase propensity to osteoporosis (Friberg *et al.*, 1974). Work in mice suggests that the bone deformities result from Cd deposition in bone tissue, leading to interference with calcification, decalcification and bone remodelling (Wang and Bhattacharyya, 1993) and Cd has been shown to have an inhibitory effect on vitamin D-stimulated calcium transport in rats (Ando *et al.*, 1981). Studies of enhanced dietary Zn intake in male rats chronically exposed to Cd suggest that Zn supplementation may have a protective influence on bone tissue biomechanical properties, and thus decrease bone fractures (Brzóska *et al.*, 2008).

It is widely accepted that high concentrations of molybdenum (Mo) results in a Cu deficient status (Mills *et al.*, 1977), high concentrations of dietary Zn have also been shown to be antagonistic to copper status (Grant-Frost and Underwood, 1958). The effects are only seen at high Zn intakes, such as those with environmental exposure of Zn in the vicinity of certain types of industries, and exacerbated by low Cu diets (Hill and Matrone, 1970). Interestingly, Cd has been demonstrated to be much more potent inhibitor of Cu metabolism; exerting an almost 100-fold increased effect on Cu metabolism (Davies and Campbell, 1977; Hall *et al.*, 1979). Dietary Cd fed to sheep has been

reported to decrease liver concentrations of Cu (Mills and Dalgarno, 1972; Doyle and Pfander, 1975). Whilst, Bremner and Campbell (1978) suggests that the adverse effects of Cd exposure can be improved by supplementation with Cu. Interestingly, in sheep, increased dietary Mo (up to 15.45 mg/kg DM) and sulphur (S) (up to 5.9 mg/kg DM) decreased the accumulation of Cd (fed at 4 mg/kg DM) in tissues (Smith and White, 1997).

In humans, pregnancy Fe deficiency is correlated with increased Cd adsorption and body burden (Akesson *et al.*, 2002), however, Cd uptake was not higher in Fe deficient suckling piglets. In these piglets DMT1, FPN1 and MT expression was similar in both Fe and non-Fe deficient piglets (Öhrvik *et al.*, 2007).

A review conducted by Peraza *et al.* (1998) suggests that toxicity of Cd may result from disturbances with Zn metabolism; inadequate Zn containing diets may contribute to the development of Cd toxicity at lower Cd exposure. Cadmium has an inhibitory effect on Zn containing enzymes, including carboxypeptidase, and α -mannosidase; it also has the ability to replace zinc in MT (reviewed by Peraza *et al.*, 1998). The addition of Zn (100 ppm) to calves fed diets containing either 40 or 160 ppm Cd tended to increase feed consumption, weight gains, testicle size, haemoglobin and blood zinc concentrations, suggesting that the addition of Zn partially offset the effects of Cd on calf performance (Powell *et al.*, 1964).

Selenium (Se) has been shown to play a role in Cd toxicity (reviewed by Peraza *et al.*, 1998). It is believed that Se has the ability to alter the binding of Cd from MT to higher weight proteins thus allowing the MT to bind essential elements including Zn and Cu. Parizek (1978) described the protective effect of Se against Cd administered concurrently. The decrease in toxicity was associated with increased blood and blood plasma concentrations of both Cd and Se.

The relative importance of other elements in relation to Cd toxicity is highlighted in the well known case of Itai-itai like diseases which seem to occur only in Asia, where the high Cd uptake of rice was accompanied by low concentrations of Ca, Fe and especially Zn. All of which are probably strong contributing factors that influence the absorption of Cd and exacerbate Cd-related health effects (Lalor, 2008).

The effect of Cd on growth rates

Variable effects on Cd on animal growth have been reported. While studies examining the effect of oral Cd exposure in weanling rats has shown no affect on weight (Bebe *et al.*, 1996; research

conducted in growing ruminants suggests that Cd has a negative effect on growth rates (Powell *et al.*, 1964; Doyle *et al.*, 1974; Lynch *et al.*, 1976; Masaoka *et al.*, 1989). Work conducted by Masaoka *et al.* (1989) examined the effect of feeding S (10 g S/kg ration) with Cd (3 mg Cd/kg ration) to growing dairy bulls, S alone decreased daily gains by 15 %, while the combination of S and Cd decreased daily gains by 19 %. Monogastrics have been shown to be similarly affected; pigs fed the same combination of S and Cd experienced a 17 % decrease in growth rates (Anke *et al.*, 1989). However, an earlier study reported that feeding dietary Cd (up to 11.3 mg Cd/kg ration for a 3 month period) did not decrease body weight of cows (Sharma *et al.*, 1979). However, cows were only exposed to Cd for such a short period of time and considering that these cows had already achieved adult body weight, the results must be considered less relevant. In the same study, feeding Cd at the higher rate, the growth rate in pigs decreased, but only two animals were finished up this study and hence its findings are questionable. Blood concentrations of Cd were not reported in the Sharma *et al.* (1979) study. In a study examining the effect of high concentrations dietary Cd (15 mg Cd/kg bodyweight daily) and/or lead (up to 18 mg Pb/kg bodyweight daily), on male Holstein calves, feed intake and body weights decreased during the six-week feeding period when Cd alone was fed, with Cd-fed calves weighing a mean (\pm SD) of 71.4 ± 10.5 kg compared with a 92 ± 12.5 kg for control calves (Lynch *et al.*, 1976). Calves in this study weighed on average 61 kg at the beginning of this trial, suggestive that mean average daily gains were 0.74 and 0.25 kg/day for the control and Cd-fed calves respectively. While an earlier study conducted by Powell *et al.* (1964) reported very severe growth retardation when male calves (Holstein and Jersey) were fed a high dose of Cd (640 mg Cd/kg ration), while, a dose of 160 mg Cd/kg ration also depressed growth rates, to a lesser extent, to 0.73 kg/day (Cd-fed; 640 mg Cd/kg ration) compared with 1.04 kg/day (controls). One of the four calves receiving the 640 mg Cd/kg ration dose died after six weeks. A diet of 40 mg Cd/kg ration decreased growth rates numerically (0.87 compared with 1.04 kg/day for Cd-fed and controls, respectively, but this was not statistically significant. All four calves given a dose of 2560 mg Cd/kg ration did not gain weight and died at various stages within 8 weeks. The calves receiving the 2560 and 640 mg Cd/kg ration displayed clinical signs of Cd toxicity that developed over a period of 16 to 64 days; unthrifty appearance, rough coat hair, dry scaly skin, dehydration, loss of hair from legs, thighs, ventral chest, and brisket, mouth lesions, oedematous, shrunken scaly scrotum, sore and enlarged joints, impaired sight, extreme emaciation and some atrophy of hind limb muscles. All of these studies highlight the short-term effect of high Cd exposure in growing cattle, and the toxicity of higher doses.

Effect of Cd on gastrointestinal tract

Studies in rats suggest that the digestive and absorptive capacity of small intestine is not significantly affected by oral administration of Cd chlorides, even up to oral doses of 0.3 and 1 mmol Cd/kg and that proximal impairments may be compensated by unaltered distal function. Despite the resultant high Cd concentration in the mucosa, most enzyme activity was not altered (Elsenhans *et al.*, 1999). However, the authors did speculate that since the proximal portion of the gastrointestinal tract was most affected, the absorption of micronutrients e.g. Fe, through impaired proximal function may be an critical.

Effect of Cd on haematological parameters

Cadmium is one of many factors reported to result in a spectrum of pathophysiological conditions that directly or indirectly alter red blood cell (RBC) production (Berlin and Friberg 1960, Berlin and Piscator 1961, Fox *et al.* 1971). The production of RBC is dependent on the formation of haemoglobin (Hgb); an important rate-limiting step during erythropoiesis (Neuwirt *et al.* 1976). The enzyme delta-aminolevulinic acid dehydratase (ALAD) plays a key role in Hgb formation and its activity is an indicator of the rate of Hgb synthesis. However, Cd effects on ALAD are conflicting. Cadmium has been demonstrated to increase (bovine RBCs; Wilson *et al.* 1972), decrease (Abdulla and Haeger-Aronsen 1971; Lynch *et al.*, 1976) or not alter (human RBCs; Roels *et al.* 1975) ALAD. Variable effects of Cd on Hgb have been reported (Powel *et al.*, 1964), lower doses of dietary Cd decreased Hgb compared with high doses. The study conducted by Lynch *et al.* (1976) reported no effect of high concentrations of dietary Cd on Hgb compared with control calves. Work conducted by Hogan and Jackson (1986) reported that Cd increased RBC production in mice, while other workers have reported the development of microcytic anaemia (Fox *et al.*, 1971) and decreased circulatory time of RBCs (Berlin and Friberg, 1960). While further work conducted by Hogan and Ranzick (1992) using mice suggests that intraperitoneal Cd, given at a dosage rate of 2 mg/kg body weight, as a single injection, or at 1 mg/kg given at 12 or 24 h intervals, is an effective activator of ALAD, while Cd given at intervals of greater than 24 h did not affect ALAD, suggesting that duration of exposure may affect the response to Cd. Eosinophilia has also been associated with Cd intoxication (reviewed by Martelli *et al.*, 2006).

Effect of Cd on bone

Many studies allude to the adverse effect of Cd exposure on bone health (Alfvén *et al.*, 2002; 2004). The Swedish OSCAR (Osteoporosis-Cd as a risk factor) study, conducted on people (n = 1021) aged between 16 and 81 years, exposed to environmental or occupational Cd revealed using multiple linear regression analysis that older subgroups (persons greater than 60 years; n = 348)

with high blood Cd concentrations (greater than 10 nmol/l Cd, equivalent to 1.12 µg/kg) had a 2.9 fold (CI 1.4 – 5.8) greater risk of low bone mineral density (Alfvén *et al.*, 2002) while subjects greater than 50 years with high urinary Cd creatinine ratio (> 4 nmol Cd/mmol creatinine) had an 8.8 fold (CI 2.6 – 30) risk of distal upper limb fracture (Alfven *et al.*, 2004).

Conclusions

Cadmium is considered to be one of the most toxic substances in the environment due to its wide range of organ toxicity and long elimination half-life. Cadmium pollution may result from a number of different activities, including industrial processing, mining, and agricultural practices. Its long half-life and its ability to accumulate in the liver and kidneys are evident. The importance of interactions between Cd, a non-essential element, with essential trace elements has been highlighted; especially the interactions between Cd and Ca, Fe, Zn, Se and Cu. It is clear that Cd has the ability to effect changes on a wide spectrum of pathophysiological functions in animals, including alterations to bone metabolism, RBC production, kidney function, animal growth and development.

References

- Abdulla M, Haeger-Aronsen B 1971 ALA-dehydratase activation by zinc Enzyme 12:708-710
- Agency for Toxic Substances and Diseases Registry 2008 CERCLA Priority List of Hazardous Substances viewed on-line at <http://www.atsdr.cdc.gov/cercla/07list.html>
- Akesson A, Berglund M, Schutz A, Bjellerup P, Bremme K, Vahter M 2002 Cd Exposure in Pregnancy and Lactation in Relation to Iron Status. *Am J Public Health* 92, 284-287.
- Alfvén T, Järup L, Elinder C-G 2002 Cd and lead in blood in relation to low bone mineral density and tubular proteinuria *Environ Health Perspect* 110: 699-702
- Alfvén T, Elinder C-G, Hellström L, Lagarde F, Järup L 2004 Cd exposure and distal forearm fractures *J Bone Min Res* 19: 900-905
- Ando M, Shimizzu M, Sayato Y, Tanimura A, Tobe M 1981 The inhibition of vitamin D-stimulated intestinal calcium transport in rats after continuous oral administration of Cd *Toxicol Appl Pharmacol* 61: 297-301
- Anke M, Masaoka T, Groppe B, Zervas G, Arnhold W 1989 The influence of sulphur, molybdenum and Cd exposure on the growth of goats, cattle and pigs *Arch Tierernahr* 39: 221-228
- Bebe FN, Panemangalore MS, Panemangalore M 1996 Modulation of tissue trace metal concentrations in weanling rats fed different levels of zinc and exposed to oral Cd *Nutr Res* 16: 1369-1380

- Berglund M, Akesson A, Nermell B, Vahter M 1994 Intestinal absorption of dietary Cd in woman depends on body iron stores and fiber intake *Environ Health Prospect* 102: 1058-1066
- Berlin M, Friberg L 1960 Bone-marrow activity and erythrocyte destruction in chronic Cd poisoning. *Arch Environ Hlth* 1:478-486.
- Berlin M, Piscator M 1961 Blood volume in normal and Cd poisoning rabbits *Arch Environ Hlth* 2:100-107
- Bremner I 1979 Symposium on metal toxicities *Proc Nutr Soc* 38: 235-242
- Bremner, I., Campbell, J.K., 1978, Effect of Copper and Zinc Status on Susceptibility to Cadmium Intoxication. *Environ Health Perspectives* 25, 125-128
- Bressler, J.P., Olivi, L., Cheong, J.H., Kim, Y., Bannon, D., 2004, Divalent metal transporter 1 in lead and Cd transport. *Annals of the New York Academy of Sciences* 1012, 142-152.
- Blanco-Penedo, I., Cruz, J.M., López-Alonso, M., Miranda, M., Castillo, C., Hernández, J., Benedito, J.L., 2006, Influence of copper status on the accumulation of toxic and essential metals in cattle. *Environment International* 32, 901-906
- Brzóska, M.M., Moniuszko-Jakoniuk, J., 2005, Disorders in bone metabolism of female rats chronically exposed to Cd. *Toxicology and Applied Pharmacology* 202, 68-83.
- Campbell JK, Mills CF 1974 Effect of dietary cadmium and zinc on rats maintained on diets low in copper *Proc Nutr Soc* 33: 15A-17A
- Cai, Q., Long, M.-L., Zhu, M., Zhou, Q.-Z., Zhang, L., Liu, J., 2009, Food chain transfer of cadmium and lead to cattle in a lead-zinc smelter in Guizhou, China. *Environmental Pollution* In Press, Corrected Proof doi:10.1016/j.envpol.2009.05.048.
- DAF 2000. Assessment of the risks to health and the environment from cadmium on phosphatic fertilisers for South East region of Ireland. (Dublin, Department of Agriculture, Food and Rural Development)
- Davies NT, Campbell JK 1977 The effect of cadmium on intestinal copper absorption and binding in the rat. *Life Sci* 20: 955-960
- Doganoc, D.Z., 1996, Lead and cadmium concentrations in meat, liver and kidney of Slovenian cattle and pigs from 1989 to 1993. *Food Additives and Contaminants* 13, 237-241
- Dorian, C., Gattone, V.H., Klaassen, C.D., 1995, Discrepancy between the nephrotoxic potencies of cadmium-metallothionein and cadmium chloride and the renal concentration of cadmium in the proximal convoluted tubules. *Toxicology and Applied Pharmacology* 130, 161-168
- Doyle JJ Phander WH 1975 Interactions of cadmium with copper, iron, zinc, and manganese in ovine tissues *J Nutr* 105: 599-606
- Doyle JJ Phander WH, Grebing SE, Pierce JO 1974 Effect of dietary Cd on growth, Cd absorption and Cd tissue levels in growing lambs *J Nutr* 104: 160-166

- EC., Commission regulation (EC) No 629/2008 of 2 July 2008 amending Regulation (EC) No 1881/2006 setting maximum levels for certain contaminants in foodstuffs. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:173:0006:0009:EN:PDF>
- EC., Commission regulation (EC) No 1881/2006 of 19 December 2006 setting maximum levels for certain contaminants in foodstuffs. http://eur-lex.europa.eu/LexUriServ/site/en/oj/2006/l_364/l_36420061220en00050024.pdf
- EFSA, Cadmium in food. Scientific opinion of the panel on contaminants in the food chain. The EFSA Journal 980, 23-139, 2009.
- El Heni J, Messaoudi I, Hamouda F, Abdelhamid K 2008 protective effects of selenium (Se) and zinc (Zn) on Cd (Cd) toxicity in the liver and kidney of the rat: histology and Cd accumulation *Food Chem Toxicol* 46: 3522-3527
- Elinder CG, Kjellstrom T, Lind B, Linnman L, Piscator M, Sundsdotter K 1983 Cd exposure from smoking cigarettes: variation with time and country where purchased *Environ Res* 32: 220-227
- Elsenhans B, Hunder G, Strugala G, Schumann K 1999 Longitudinal pattern of enzymatic and absorptive functions in the small intestine of rats after short term exposure to dietary Cd chloride *Arch Environ Contam Toxicol* 36: 341-346
- Ericson JE, Smith DR, Flegal AR 1991 Skeletal concentrations of lead, Cd, zinc, and silver in North American Pecos Indians *Environ Health Perspect* 93: 217-223
- Farmer, A.A., Farmer, A.M., 2000, Concentrations of cadmium, lead and zinc in livestock feed and organs around a metal production centre in eastern Kazakhstan. *The Science of The Total Environment* 257, 53-60.
- Falandysz, J., 1993, Some toxic and essential trace metals in cattle from the northern part of Poland. *The Science of The Total Environment* 136, 177-191.
- Fay, D., Kramers, G., Zhang, C., McGrath, D., Grennan, E., 2007, Soil geochemical atlas of Ireland. Colourbooks Ltd., Dublin, Ireland.
- Filipic M, Fatur T, Vudrag 2006 Molecular mechanisms of Cd induced mutagenicity *Hun Exp Toxicol* 25: 67-77
- Friberg L, Piscator M, Nordberg GF, Kjellstrom T 1974 Cd in the environment 2nd Edition, CRC Press, Cleveland, OH, USA
- Foihirun K, Wongwit W, Kaewkungwal J, Ramasoota P, Sangdee P 2006 Preparation of *in vivo* cow control blood samples for Cd Analysis *Southeast Asian J Trop Med Public Health* 37: 544-548
- Fox MRS, Fry EE Jr, Harland BF, Schetel ME, Weeks CE 1971 Effect of ascorbic acid on Cd toxicity in the young coturnix *J Nutr* 101:1295-1306

- George, S., Coombs, T., 1977, The effects of chelating agents on the uptake and accumulation of cadmium by *Mytilus edulis*. *Marine Biology* 39, 265-268
- Grill, E., Winnacker, E.L., Zenk, M.H., 1987, Phytochelatins, a class of heavy-metal-binding peptides from plants, are functionally analogous to metallothioneins. *Proceedings of the National Academy of Science* 84, 439 - 443
- Goyer RA 1995 Nutrition and Metal toxicity *Am J Clin Nutr* 61(Suppl): 646-650S
- Goyer RA, Cherian MG 1992 Role of metallothionein in human placenta and rats exposed to Cd
In: Cd in the human environment: toxicity and carcinogenicity Nordberg GE, Heber RF, Alessio L (Eds) IARC, Lyon France pp 199-210
- Grant-Frost DR, Underwood EJ 1958 Zinc toxicity in the rat and its interrelation with copper. *Aust J Exp Biol* 36: 339
- Griffiths, W.J., Kelly, A.L., Smith, S.J., Cox, T.M., 2000, Localisation of iron transport and regulatory proteins in human cells. *QJM* 93, 575-587
- Hall AC, Young BW, Bremner I 1979 Intestinal metallothionein and the mutual antagonism between copper and zinc in the rat. *J Inorg Biochem* 11: 57-66.
- Han, O., Fleet, J.C., Wood, R.J., 1999, Reciprocal regulation of HFE and Namp2 gene expression by iron in human intestinal cells. *Journal of Nutrition* 129, 98-104
- Hill CH, Matrone G 1970 Chemical parameters in the study of in vivo and in vitro interactions of transition elements. *Fed. Proc.* 29: 1474-1481
- Hogan GR, Jackson PD 1986 Dichotomous effects of Cd and selenium in erythropoiesis in mice *Bull Environ Contam Toxicol* 36: 674-679
- Hogan GR, Razniak SL 1992 Split dose studies on the erythropoietic effects of Cd *Bull Environ Contam Toxicol* 48: 857-801
- Horiguchi, H., Kayama, F., Oguma, E., Willmore, W.G., Hradecky, P., Bunn, H.F., 2000, Cd and platinum suppression of erythropoietin production in cell culture: clinical implications. *Blood* 96, 3743-3747.
- Houpert, P., Mehennaoui, S., Joseph-Enriquez, B., Federspiel, B., Milhaud, G., 1995, Pharmacokinetics of cadmium following intravenous and oral administration to non-lactating ewes. *Veterinary Research* 26, 145-154.
- Houpert, P., Federspiel, B., Milhaud, G., 1997, Toxicokinetics of Cadmium in Lactating and Nonlactating Ewes after Oral and Intravenous Administration. *Environmental Research* 72, 140-150.
- Järup, L., 2003, Hazards of heavy metal contamination. *British Medical Bulletin* 68, 167-182.
- Jonah, M.M., Bhattacharyya, M.H., 1989, Early changes in the tissue distribution of cadmium after oral but not intravenous cadmium exposure. *Toxicology* 58, 325-338

- Jorhem, L., Slorach, S., Sundström, B., Ohlin, B., 1991, Lead, Cadmium, arsenic and mercury in meat, liver and kidney of Swedish pigs and cattle in 1984-88. *Food Additives and Contaminants* 8, 201-211.
- Klaassen CD, Liu J, Diwan BA, 2009, Metallothionein protection of Cd toxicity. *Toxicology and Applied Pharmacology* 238, 215-220
- Kreis IA, de Does M, Hoekstra JA, de Lezenne Coulander C, Peters PW, Wentink GH 1993 Effects of Cd on reproduction, an epizootological study *Teratology* 48: 189-196
- Lalor GC, Rattray R, Simpson P, Vutchkov MK 1998 Heavy metals in Jamaica soils. Part 3: the distribution of Cd in Jamaican soils *Rev Int Comtam Ambient* 14: 7-12
- Lalor, G., 2008, Review of Cd transfers from soil to humans and its health effects in the Jamaican environment. *Science of The Total Environment* 400, 162-172
- Langlands JP, Donald GE, Bowles JE 1988 Cd concentrations in liver, kidney, and muscle in Australian sheep and cattle *Aust K Exp Agric* 28: 291-297
- López Alonso, M., Montaña, F.P., Miranda, M., Castillo, C., Hernández, J., Benedito, J.L., 2004, Interactions between toxic (As, Cd, Hg and Pb) and nutritional essential (Ca, Co, Cr, Cu, Fe, Mn, Mo, Ni, Se, Zn) elements in the tissues of cattle from NW Spain. *BioMetals* 17, 389-397.
- López Alonso, M., Benedito, J.L., Miranda, M., Castillo, C., Hernández, J., Shore, R.F., 2000, Arsenic, cadmium, lead, copper and zinc in cattle from Galicia, NW Spain. *The Science of The Total Environment* 246, 237-248.
- Lopez Alonso M 1999 Principales elementos contaminantes en ganado vacuno de Galicia. Thesis, University of Santiago de Compostela
- Liu, Z.P., 2003, Lead poisoning combined with cadmium in sheep and horses in the vicinity of non-ferrous metal smelters. 309, 117-126
- Lynch GP, Smith DF, Fisher M, Pike TL, Weinland BT 1976 Physiological responses of calves to Cd and lead *J Anim Sci* 42: 410-421
- Martelli A, Rousselet E, Dycke C, Bouron A, Moulis J-M 2006 Cd toxicity in animal cells by interference with essential metals *Biochimie* 88: 1807-1814
- Masaoka T, Anke M, Groppe B, Akahori F 1989 Effects of sulphur, molybdenum and Cd on the growth rate and trace element status in the ruminants and pigs *6th Intl Trace Element Symp* 2: 510-525
- Mills CF, Dalgarno AC 1972 Copper and zinc status of ewes and lambs receiving increased dietary concentrations of Cd *Nature* 239: 171-176
- Mills, C.F., Dalgarno, A.C., Bremner, I. & ElGallad, T.T. 1977. Influence of the dietary content of molybdenum and sulphur upon hepatic retention of copper in young cattle. *Proceedings of*

the Nutrition Society, 36, 106A.

- Min, K.-S., Fujita, Y., Onosaka, S., Tanaka, K., 1991, Role of intestinal metallothionein in absorption and distribution of orally administered cadmium. *Toxicology and Applied Pharmacology* 109, 7-16
- Min, K.-S., Nakatsubo, T., Kawamura, S., Fujita, Y., Onosaka, S., Tanaka, K., 1992, Effects of mucosal metallothionein in small intestine on tissue distribution of cadmium after oral administration of cadmium compounds. *Toxicology and Applied Pharmacology* 113, 306-310.
- Miranda M, Lopez-Alonso M, Castillo C, Hernandez J Benedito JL 2005 Effects of moderate pollution on toxic and trace metal levels in calves from a polluted area in northern Spain *Environ Int* 31: 543-548
- Miranda M, Lopez-Alonso M, Castillo C, Hernandez J Benedito JL 2001 Cd levels in liver, kidney and meat in calves from Asturias (North Spain) *Eur Food Res Technol* 212: 426-430
- Neuwirt J, Ponka P, Borova J 1976 In Erythropoiesis, Nakao K, Fisher JW, Takaky F (eds). University Park Press, Baltimore, MD, p 413-421
- Niemi, A., Venäläinen, E.-J., Hirvi, T., Hirn, J., Karppanen, E., 1991, The lead, cadmium, and mercury concentrations in muscle, liver and kidney from Finnish pigs and cattle during 1987-1988. *Zeitschrift für Lebensmittel Untersuchung und Forschung* 192, 427-429.
- NRC, 2005, Mineral Tolerances of Animals, Second Edition. National Academic Press, Washington DC, USA
- NRC 1980 Mineral tolerance of domestic animals national Academy of Sciences, Washington, DC, USA
- Nriagu J, Boughanen M, Linder A, Howe Andrea, Grant C, Rattray R, Vutchkov M, Lalor G 2009 levels of As, Cd, Pb, Cu, Se and Zn in bovine kidneys and livers in Jamaica *Ecotoxicol Environ Safety* 72: 564-571
- Noda M, Kitagawa M 1990 A quantitative study of iliac bone histopathology on 62 cases with itai-itai disease *Calcif Tissue Int* 47: 66-74
- Nordberg GF, Kjellstrom T, Norberg M 1985 Kinetics and metabolism In: Cd and Health: A toxicological and epidemiological appraisal Vol 1: Exposure dose and metabolism Friberg L, Elinder CG, Kjellstrom (Eds) Boca Raton, CRC Press pp 103-178
- Öhrvik H, Oskarsson A, Lundh T, Staffan Skerfving S, Tallkvist J 2007 Impact of iron status on Cd uptake in suckling piglets. *Toxicology* 240, 15-24
- Palminger Hallen I, Jorhen L, Json Lagerkvist B, Oskarsson A 1995 Lead and Cd levels in human milk and blood *Sci Tot Environ* 166: 149-155

- Parizek, J., 1978, Interactions between selenium compounds and those of mercury or Cd. *Environ Health Perspect* 25, 53-55
- Park, J.D., Cherrington, N.J., Klaassen, C.D., 2002, Intestinal absorption of cadmium is associated with divalent metal transporter 1 in rats. *Toxicological Science* 68, 288-294
- Patra RC, Swarup D, Naresh R, Kumar P, Nandi D, Shekhar P, Roy S, Ali SL 2007 Tail hair as an indicator of environmental exposure of cows to lead and Cd in different industrial areas *Ecotoxicol Environ Safety* 66: 127-131
- Patra RC, Swarup D, Sharma MC, Naresh R 2006 Trace mineral profile in blood and hair from cattle environmentally exposed to lead and Cd around different industrial units *J Vet Med* 53: 511-517
- Patra RC, Swarup D, Naresh R, Kumar P, Shekhar P, Ranjan R 2005 Cd level in blood and milk from animals reared around different polluting sources in India *Bull Environ Contam Toxicol* 74: 1092-1097
- Patrick, L., 2009, Toxic metals and antioxidants: part II, the role of antioxidants in arsenic and cadmium toxicity. *Alternative Medicine Review* 8, 106-128
- Peraza, M.A., Ayala-Fierro, F., Barber, D.S., Casarez, E., Rael, L.T., 1998, Effects of micronutrients on metal toxicity. *Environ Health Perspect* 106, 203-216
- Penumarthi, L., Oehme, F.W., Hayes, R.H., 1980, Lead, cadmium, and mercury tissue residues in healthy swine, cattle, dogs, and horses from the midwestern United States *Archives of Environmental Contamination and Toxicology* 9, 193-206
- Pope A, Rall DP *Environmental Medicine. Integrating a missing element into medical education* National Academy Press, Washington DC, USA pp 230-231
- Powell GW, Miller WJ, Morton JD, Clifton CM 1964 Influence of dietary Cd level and supplemental zinc on Cd toxicity in the bovine *J Nutr* 84: 205-213
- Rahimi, E., Rokni, N., 2008, Measurement of cadmium residues in muscle, liver and kidney of cattle slaughtered in Isfahan abattoir using graphite furnace atomic absorption spectrometry (GFAAS): A preliminary study. *Iranian Journal of Veterianry Research* 9, 174-177.
- Reeves PG, Chaney RL 2004 Marginal nutritional status of zinc, iron, and calcium increases Cd retention in the duodenum and other organs of rats fed rice-based diets *Environ Res* 96: 311-22
- Reeves PG, Chaney RL 2002 Nutritional status affects the absorption and whole-body and organ retention of Cd in rats fed rice-based diets. *Environ Sci Technol.* 2002 15: 2684-2689
- Reeves PG, Chaney RL 2001 Mineral status of female rats affects the absorption and organ distribution of dietary Cd derived from edible sunflower kernels (*Helianthus annuus* L.) *Environ Res* 85: 215-2

- Roberts, A.H.C., Longhurst, R.D., Brown, M.W., 1994, Cadmium status of soils, plants and grazing animals in New Zealand. *New Zealand Journal of Agricultural Research* 37, 119-129.
- Roels HA, Buchet JP, Launergs RR, Sonnet J 1975 Comparison of *in vivo* effect of inorganic lead and Cd on glutathione reductase system and delta amino levulinate dehydratase in human erythrocytes *Brit J Ind Med* 32:181-192
- Sedki, A., Lekouch, N., Gamon, S., Pineau, A., 2003, Toxic and essential trace metals in muscle, liver and kidney of bovines from a polluted area of Morocco. *The Science of The Total Environment* 317, 201-205.
- Sharma RP, Street JC, Verna MP, Shupe JL 1979 Cd uptake from feed and its distribution to food products of livestock *Environ Health Perspect* 28: 59-66
- Smith GM White CL 1997 A molybdenum-sulfur-Cd interaction in sheep *Aust J Agric Res* 48: 147-154
- Spivey Fox 1987 Assessment of Cd, lead and vanadium status of large animals as related to the human food chain *J Anim Sci* 65: 1744-1752
- Spierenburg, T.J., de Graaf, G.J., Baars, A.J., 1988, Cadmium, zinc, lead and copper in livers and kidneys of cattle in the neighbourhood of zinc refineries. *Environmental Monitoring and Assessment* 11, 107-114.
- Sunderman, F.W., Jr., 2001, Nasal Toxicity, Carcinogenicity, and Olfactory Uptake of Metals. *Ann Clin Lab Sci* 31, 3-24.
- Suzuki, T., Momoi, K., Hosoyamada, M., Kimura, M., Shibasaki, T., 2007, Normal cadmium uptake in microcytic anemia mk/mk mice suggests that DMT1 is not the only cadmium transporter in vivo. *Toxicology and Applied Pharmacology* 227, 462-467
- Swarup D, Naresh R, Vaeshney VP, Balagangatharathilagar M, Kumar P, Nandi D, Patra RC 2007 Changes in plasma hormones profile and liver function in cows naturally exposed to lead and Cd around different industrial areas *Res Vet Sci* 82: 16-21
- Tahvonen, R., Kumpulainen, J., 1994, Lead and cadmium contents of pork, beef and chicken, and in pig and cow liver in Finland during 1991. *Food Additives and Contaminants* 11, 415-426.
- Tallkvist J, Bowlus CL, Lönnerdal B 2001 DMT1 gene expression and Cd absorption in human absorptive enterocytes. *Toxicology Letters* 122, 171-177.
- Telford JN, Thonney ML, Hogue DE, Stouffer JR, Bache CA, Gutemann WH, Lisk DJ, Babish JG, Stoewsand GS 1982 Toxicological studies in growing sheep fed silage corn cultured on municipal sludge-amended acid subsoil *J Toxicol Environ Health* 10: 73-85

- Trinder, D., Oates, P.S., Thomas, C., Sadleir, J., Morgan, E.H., 2000, Localisation of divalent metal transporter 1 (DMT1) to the microvillus membrane membrane of rat duodenal enterocytes in iron deficiency, but to hepatocytes in iron overload. *Gut* 46, 270-276
- Underwood, E.J., 1977, Trace Elements in Human and Animal Nutrition, 4th Edition. Academic Press, New York
- US Department of Health, Education and Welfare 1966 Cited by Dorn RC, Cd: a review *FDA Report* 3526-76F, June 1976
- Veling J, Counotte GH. 1995 Selenium deficiency without clinical symptoms in young cattle on a dairy farm *Tijdschr Diergeneeskd* 120: 464-465
- Wang C, Bhattacharyya MH 1993 Effects of cadmium on bone calcium and ⁴⁵Ca in nonpregnant mice on a calcium-deficient diet: evidence of direct effect of cadmium on bone, *Toxicol. Appl. Pharmacol.* 120 (1993), pp. 228–239
- Wasowicz W, Gromadzinska J, Rydzynski K 2001 Blood concentration of essential trace elements and heavy metals in workers exposed to lead and Cd *Int J Occup Med Environ Health* 14: 223-229
- W.H.O, 1992, IPCS. Environmental health criteria 134 Cadmium. Geneva, World Health Organisation.
- Wilson, A.K., Bhattacharyya, M.H., 1997, Effects of cadmium on bone: An *in vivo* model for the early response. *Toxicology and Applied Pharmacology* 145, 68-73
- Wilson EL, Burger PE, Dowdle EB 1972 Beef-liver delta-amino levulinic acid dehydratase: Purification and properties *Eur J Biochem* 29:563-571
- Włostowski, T., Bonda, E., Krasowska, A., 2006, Free-ranging European bisons accumulate more cadmium in the liver and kidneys than domestic cattle in north-eastern Poland. *Science of The Total Environment* 364, 295-300.
- Zasadowski, A., Barski, D., Markiewicz, K., Zasadowski, Z., Spodniewska, A., Terlecka, A., 1999, Levels of cadmium contamination of domestic animals (cattle) in the region of Warmia and Masuria. *Polish Journal of Environmental Studies* 8, 443-446.