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 border 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 DMT1 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 DMT1 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 metallothioein 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. Metallothioein expression however was not affected by Fe status in piglets (Öhrvik et al., 2007). Induction of metallothioein 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 (Brzó ska 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 ± SD 0.85 μg/l compared with 10 ± 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 (Foighurun 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.

<table>
<thead>
<tr>
<th>Country</th>
<th>Animal</th>
<th>Age</th>
<th>Liver Cd</th>
<th>Kidney Cd (*cortex only)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU Member States</strong></td>
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<tr>
<td>Poland</td>
<td>Bison (Free ranging)</td>
<td>1yr</td>
<td>0.09±0.01 (0.07-0.10)</td>
<td>0.21±0.03 (0.18-0.25)</td>
<td>Wlostowski et al., 2006</td>
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<tr>
<td></td>
<td></td>
<td>2yr</td>
<td>0.22±0.1 (0.10-0.35)</td>
<td>0.41±0.07 (0.35-0.50)</td>
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<tr>
<td></td>
<td></td>
<td>4yr-6yr</td>
<td>0.43±0.03 (0.40-0.48)</td>
<td>1.24±0.38 (0.86-1.82)</td>
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<td></td>
<td></td>
<td>7yr-12yr</td>
<td>0.45±0.08 (0.31-0.58)</td>
<td>2.79±0.66 (1.95-3.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Domestic cattle</td>
<td>8yr-12yr</td>
<td>0.2±0.06 (0.09-0.27)</td>
<td>1.30±0.47 (0.68-2.0)</td>
<td></td>
</tr>
<tr>
<td>Poland</td>
<td>Cattle</td>
<td>&lt;2yrs</td>
<td>0.159±0.098 (0.06-0.487)</td>
<td>0.425±0.195 (0.104-0.937)</td>
<td>Zasadowski et al., 1999</td>
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<tr>
<td></td>
<td></td>
<td>&gt;2yrs</td>
<td>0.263±0.166 (0.081-0.672)</td>
<td>1.703±1.106 (0.59-4.275)</td>
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</tr>
<tr>
<td>Poland</td>
<td>Cattle</td>
<td></td>
<td>0.12</td>
<td>0.61</td>
<td>Falandysz, 1993</td>
</tr>
<tr>
<td>NW Spain</td>
<td>Cows</td>
<td>3yr-16yr</td>
<td>0.0547 (0.013-0.564)</td>
<td>*</td>
<td>López-Alonso et al., 2004</td>
</tr>
<tr>
<td>NW Spain</td>
<td>Calves</td>
<td>6mth-10mths</td>
<td>0.00756-0.00798 (ND-7.99)</td>
<td>0.0513-0.0579 (0.00243-1.302)</td>
<td>López-Alonso et al., 2000</td>
</tr>
<tr>
<td>Spain</td>
<td>Cattle</td>
<td>2yr-16yr</td>
<td>0.0833 (0.0234-0.246)</td>
<td>0.388 (0.110-1.346)</td>
<td></td>
</tr>
<tr>
<td>N Spain</td>
<td>Cattle</td>
<td>6mths-12mths</td>
<td>0.0307±0.00124</td>
<td>0.161±0.00703</td>
<td>Miranda et al., 2001</td>
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<tr>
<td></td>
<td></td>
<td>9mth-12mth</td>
<td>0.0229 (0.00643-0.221) Rural</td>
<td>0.0964 (0.0042-0.545) Rural</td>
<td>Miranda et al., 2005</td>
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<td></td>
<td>0.0296 (0.00339-0.131) Industrial</td>
<td>0.161 (0.0235-0.717) Industrial</td>
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<tr>
<td>Sweeden</td>
<td>Cattle</td>
<td>0.07</td>
<td>0.39</td>
<td>Jorhem et al., 1991</td>
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</tr>
<tr>
<td>Finland</td>
<td>Cattle</td>
<td>0.061</td>
<td>0.35</td>
<td>Niemi et al., 1991</td>
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<tr>
<td>Finland</td>
<td>Cattle</td>
<td>0.036</td>
<td></td>
<td>Tahvonen and Kumpulainen, 1994</td>
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<td></td>
<td></td>
<td>0.066</td>
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<tr>
<td>Slovenia</td>
<td>Cattle</td>
<td>0.094</td>
<td>0.373</td>
<td>Doganoc, 1996</td>
<td></td>
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<tr>
<td>Netherlands</td>
<td>Cattle</td>
<td>3mths-13yr</td>
<td>0.16 Control area*</td>
<td>1.61 Control area*</td>
<td>Spierenburg et al., 1988</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>0.35 Polluted area*</td>
<td>3.96 Polluted area*</td>
<td></td>
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<tr>
<td><strong>Non-EU countries</strong></td>
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<tr>
<td>Australia</td>
<td>Cattle</td>
<td>0.04-0.21</td>
<td>0.1-0.66</td>
<td>Langlands et al., 1988</td>
<td></td>
</tr>
<tr>
<td>Jamaica</td>
<td>Cattle</td>
<td>3.24 (ND-82.1)</td>
<td>7.92 (0.012-117)</td>
<td>Nriagu et al., 2009</td>
<td></td>
</tr>
<tr>
<td>Country</td>
<td>Type</td>
<td>Age</td>
<td>Conjugated</td>
<td>Albumin</td>
<td>Source</td>
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<tr>
<td>Kazakhatan</td>
<td>Cattle</td>
<td>0.05-0.79</td>
<td>0.13-1.06</td>
<td>Farmer and Farmer, 2000</td>
<td></td>
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<tr>
<td>Iran</td>
<td>Cattle</td>
<td>1yr-10yr</td>
<td>0.0497</td>
<td>0.1371</td>
<td>Rahimi and Rokni, 2008</td>
</tr>
<tr>
<td>Morocco</td>
<td>Cattle</td>
<td>1.45 (0.82-2.02)</td>
<td>4.26 (2.36-5.58)</td>
<td>Sedki et al., 2003</td>
<td></td>
</tr>
<tr>
<td>New Zealand</td>
<td>Cattle</td>
<td>Heifers</td>
<td>n/a*^2</td>
<td>&lt;0.04-0.82*^3</td>
<td>Roberts et al., 1994</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Beef cows</td>
<td>n/a*^2</td>
<td>&lt;0.04-2.06*^3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dairy cows</td>
<td>n/a*^2</td>
<td>&lt;0.04-1.65*^3</td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>Cattle</td>
<td>2yr - 4yr</td>
<td>&lt;0.5, 1.31, 2.47</td>
<td>2.15, 6.64, 38.3</td>
<td>Cai et al., 2009</td>
</tr>
</tbody>
</table>

*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 \( \alpha \)-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 (± 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, shrunkken 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 haemaglobin (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.

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