



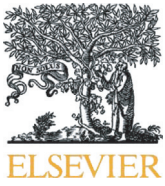
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Cadmium exposure and consequence for the health and productivity of farmed ruminants



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ABSTRACT

This paper reviews Cd exposure and consequences for the health and productivity of farmed ruminants. In farmed ruminants, Cd exposure may be associated with a number of different activities, including industrial processing, mining, and agricultural practices, and is also higher in soils in some geographic regions. Cd kidney concentrations increase with age and Cd exposure. Although Cd toxicity in farmed ruminants has been demonstrated experimentally, there are no published reports of naturally occurring Cd toxicity in farmed ruminants. Clinical signs of Cd intoxication are unlikely with a daily dietary Cd intake of less than 5 mg/kg feed, which is 5–10 times higher than the maximum permitted Cd concentration in ruminant feed in the European Union. In farmed ruminants, Cd levels in tissue are largely dependent on the Cd content of diet. However, many factors affect Cd availability, relating to soils, plants and the presence of other trace elements including Ca, Cu, Fe, Mn, Mo, Se and Zn. Experimental studies have highlighted the ability of Cd to alter trace element status, and the protective effect of good mineral status, however, there remain gaps in knowledge of the impact of these interactions on the health and productivity of farmed animals.

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1. Introduction

Cadmium is considered one of the most toxic elements in the environment, with a wide range of organ toxicity and long elimination half-life (Patrick, 2003). Industrial processing and intensive agricultural practices, resulting in the contamination of forage, feed and water, are sources of Cd exposure for farmed ruminants. In many areas, high soil Cd concentrations are the result of intensified farming methods or industrial processes. However, naturally occurring areas of high Cd concentrations in soil also occur, and some geographical areas are also associated with naturally occurring high Cd concentrations. In Europe, these are found in Ireland (Canty et al., 2011, 2014), Poland, the Goslar district in Germany and southern Sardinia (Pan et al., 2010).

Most ruminants have a low Cd burden at birth. Cd accumulates over time, primarily in kidney and liver (Underwood, 1977; Langlands et al., 1988). Cd has no known biological function but mimics the actions of other divalent metals that are essential to diverse biological functions (European Food Safety Authority, 2009). Bioavailability, retention and consequently toxicity of Cd are affected by several factors such as nutritional status (low body Fe stores) and multiple pregnancies, pre-existing health conditions or diseases (European Food Safety Authority, 2009). Cd has the ability to cross various biological membranes and, once intracellular, to bind to ligands with exceptional affinity. Cd is a known human carcinogen (reviewed by Filipic et al., 2006). However, such effects have not been described in animals and therefore will not be discussed in this paper.

This paper reviews Cd exposure and consequences for the health and productivity of farmed ruminants.

2. Cadmium exposure

2.1. Cadmium sources

Cd is a naturally occurring heavy metal present at higher concentrations in association with Cd-rich soils, including shales, oceanic and lacustrine sediments, and phosphorites. However, more than 90% of Cd in the surface environment is the result of industrial and agricultural processes (Pan et al., 2010). The combustion of coal and mineral oil, smelting, mining, alloy processing and industries that use Cd as a dye (CdS: yellow; CdSeO₃: red) in their manufacturing processes (Swarup et al., 2007) are all potential sources of Cd for farmed ruminants, with exposure decreasing with distance from the pollution source (Vos et al., 1988). More generally, 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 in industrialised cities. Cd is also a pollutant in phosphate fertilisers (Järup, 2003), leading to Cd being added to land through normal farming practice (Roberts et al., 1994; Martelli et al., 2006). The Cd content in phosphate fertilisers varies considerably, depending on source, ranging from 3.6 to 527 mg/kg phosphorous in a study conducted on fertilisers available in Australia (Satarug et al., 2003). The long-term addition of phosphate fertiliser (30 kg P/ha/annum for 31 years) in Ireland has led to a 0.07 mg/kg increase in soil Cd levels (from 0.23 to 0.30 mg/kg) in the top 10 cm of the soil (Department of Agriculture, Food and Rural Development, 2000). In the EU, Cd content in fertilisers is not currently covered by the EU Fertiliser Directive 76/116/EEC. Sewage sludge is also recognised as an important source of Cd contamination (Patrick, 2003).

In non-polluted environments, a normal and maximum soil Cd concentration of 0.1 and 0.2 mg/kg has been suggested (Brooks, 1998). In contrast, soil Cd levels of 1 mg/kg are regarded as polluted soils (Fay et al., 2007). In plants grown in a variety of naturally and artificially polluted environments (following application of sludge or wastewater, in proximity with a smelter or following application of Cd salts), Cd concentrations were variable, but consistently higher than 0.1 mg/kg. Some plants in the genus *Thalpi* are recognised as hyperaccumulator

plants, with Cd concentrations of 100 mg/kg or more in plant tissue, in particular penny-cress (*Thalpi caerulescens*) (Kirkham, 2006).

2.2. Dynamics of cadmium absorption, accumulation and detoxification

The respiratory and digestive systems have both been implicated in Cd absorption. Approximately 10 to 50% of Cd fumes are absorbed by the respiratory system. In contrast, only ~5% of oral Cd is absorbed, which is much less than similar divalent cations such as Zn and Fe. After inhalation, Cd accumulates in the olfactory bulb (Sunderman, 2001) and in cranial lung tissue (Roggeman et al., 2014). Once in the lungs, Cd can pass through alveolar cells and enter the blood stream, in contrast to other heavy metals (Bressler et al., 2004).

Wilkinson et al. (2003) present a detailed review of the accumulation of potentially-toxic metals, including Cd, by farmed ruminants. These animals can ingest Cd by consuming either contaminated herbage or soil, either following natural or artificial contamination. The concentration of Cd in herbage generally reflects that in soil, although a range of factors affect Cd availability, including soil pH, soil organic matter and plant species (Barančíková et al., 2004; Tudoreanu and Phillips, 2004; Kirkham, 2006; Phillips and Tudoreanu, 2011). Cd disperses to most root and shoot tissue, but can also be confined to the meristem. It is well recognised that antagonism between metals substantially influences Cd uptake. There are complex interactions between Cd and Zn, with Cd increasing Zn accumulation (Wilkinson et al., 2003). Further, the gastrointestinal absorption of Cd is strongly influenced by Fe status, suggesting that Cd and Fe are absorbed from the intestinal absorption through a similar mechanism (Öhrvik et al., 2007).

As a non-essential element, it is unlikely that Cd enters the body via a Cd-specific transport mechanism (Roggeman et al., 2014). Rather, Cd crosses various membranes utilising the transport mechanisms of other elements, including Ca (Martelli et al., 2006). Cd is bound to small cysteine-rich peptides, including metallothionein (MT), which are involved in the binding, transport and detoxification of excessive Cd (Nordberg et al., 1994), primarily through high affinity binding. Cd is recognised as the most important metal for MT induction in bovine kidneys (Roggeman et al., 2014). In the bloodstream, Cd is present as Cd-MT and Cd-albumin in plasma and Cd-MT in erythrocytes. Cd-MT is filtered by the kidney and re-absorbed in the proximal tubules where the complex is broken down leading to irreversible damage to tubular cells, particularly when the detoxification system is overwhelmed (Wilkinson et al., 2003). Cd is primarily stored in the liver and kidneys, which account for half of the body's total stores of Cd, with the balance in bone, pancreas, adrenals and placenta (Pope and Rall, 1995). The rate of Cd excretion, primarily in urine, is slower than that of uptake, highlighting the need for animals detoxify and store excessive Cd (George and Coombs, 1977; Wilkinson et al., 2003; Klaassen et al., 2009).

3. Cadmium concentrations in exposed animals

3.1. Blood concentrations

3.1.1. Observational studies

High blood Cd concentrations have been reported from areas of high Cd exposure. In India, cows reared and kept near a steel manufacturing plant had a mean blood Cd concentration of 232 µg/l (ranging from 90 to 410 µg/l). For comparison, a mean blood Cd concentration of 28 µg/l (ranging from not detectable to 50 µg/l) was measured in cows from a non-polluted area (Patra et al., 2005). Patra et al. (2007) reported Cd concentrations of 127 µg/l (ranging from non detectable to 410 µg/l) in cows held near a steel processing plant, compared to 25 µg/l (ranging from non detectable to 50 µg/l) in cows from a non-polluted area. Further work conducted by the same laboratory reported similar blood Cd concentrations in adult cows in another study (cattle near a steel processing plant: 230 µg/l (ranging from 90 to 410 µg/l); cattle

from a non-polluted area: 30 µg/l (ranging from non detectable to 50 µg/l); Swarup et al., 2007). However, Cd exposure is not always associated with raised blood concentrations (Miranda et al., 2005). Miranda et al. (2001) report similar Cd concentrations in cattle in industrial (0.40 µg/l; ranging from not detectable to 1.91 µg/l) and rural (0.40 µg/l; not detectable to 2.25 µg/l) areas in Asturias in northern Spain. For comparison, López Alonso et al. (2000) report mean blood Cd concentrations of 0.37 (range not presented) and 0.45 µg/l in calves and cows, respectively, in a non-polluted area of Galicia, Spain. In most of these studies, no clinical signs suggestive of ill health were reported. In one study, however, some cattle exposed to both Pb and Cd had poor skin conditions including rough hair coat, and a few were cachectic and had hyperesthesia (Swarup et al., 2007).

3.1.2. Experimental studies

Blood Cd concentrations are raised following the administration of exogenous Cd to ruminants. Daily supplementation with 15 mg Cd to male Holstein calves increased mean blood Cd concentrations to 21 ± SD 0.85 mg/l, compared with 10 ± SD 0.46 mg/l in control calves (Lynch et al., 1976). Further, Cd increased from 0.25 mg/l to 3.62 mg/l, peaking 30 to 60 min after dosing and returning to baseline by 240 minutes, when water containing a CdCl₂ solution at a dose rate of 0.06 mg Cd/kg (approximately 18 mg per animal) was given to 300 kg male *Bos indicus* cattle (Foihirun et al., 2006). Cd bioavailability (the fraction of the administered dose reaching the systemic circulation unchanged) following oral administration (CdCl₂: dosage varied by experiment, including 2 mg/kg/day for 16 days) have been estimated, being from 0.5 to 1.5% (Houpert et al., 1995) and 0.12–0.22% to 0.33–1.7% for non-lactating and lactating ewes, respectively (Houpert et al., 1997). These estimates are not dissimilar to earlier reports (0.5%, Vos et al., 1988; 5%, Doyle et al., 1974). Further, the half-time of elimination of Cd from blood varies from 101 to 151.5 days (Houpert et al., 1995). Based on these toxicokinetic data, Houpert et al. (1995) estimate that Cd blood concentrations in ewes exposed to a mean pollution consumption of 0.3 mg/kg/day would increase for 1.5–2 years, reaching a plateau of 2.9 µg/l. After removal of Cd, blood Cd concentrations would remain quantifiable for 360 ± 180 days, and detectable for 540 ± 215 days. In these experiments, approximately 0.3–0.4% of administered Cd was retained, predominantly in the liver (0.19% of administered Cd) and kidneys (0.08%) (Houpert et al., 1995).

3.2. Tissue concentrations

3.2.1. Observational studies

Table 1 summarises Cd concentrations in livers and kidneys of cattle, based on slaughterhouse studies from a range of countries. No clinical signs suggestive of ill health were reported in any of these studies. Cd kidney concentrations increased with age and in areas affected by Cd contamination. Within the EU, the highest European kidney Cd concentrations have been reported in association with areas affected by industrial pollution in Belgium (mean 2.862 mg/kg wet weight, range 0.193–15.3, Waegeneers et al., 2009a,b; 7.11 mg/kg wet weight, range 2.13–16.2, Roggeman et al., 2014) and the Netherlands (3.96 mg/kg wet weight; Spierenburg et al., 1988). In industrial areas of Spain, lower mean kidney Cd concentrations have been reported (0.161 mg/kg wet weight, Miranda et al., 2005). A mean kidney Cd concentration of 38.3 mg/kg has been reported in cattle grazing in highly polluted areas of China (Cai et al., 2009). In non-polluted areas, increased kidney Cd concentrations are associated with soil Cd concentrations (Canty et al., 2014). In Jamaica, an island known for its Cd enriched soils (Lalor et al., 1998; Lalor, 2008), Nriagu et al. (2009) report higher mean concentrations of Cd in bovine livers (3.24 mg/kg wet weight, range from not detectable to 82.1) and kidneys (7.92 mg/kg wet weight, range 0.012–117) compared with other studies.

3.2.2. Experimental studies

Cd levels in tissue are largely dependent on the Cd content of diet. Cd concentrations increase in both liver and kidneys in sheep (Rogowska et al., 2008) and cattle (Smith et al., 1991) following exogenous Cd administration. Further, there is an interaction between Cd and a range of trace elements. For example, Cd administration (1 or 5 mg/kg DM) to lactating dairy cows resulted in reduced liver Cu concentrations (Smith et al., 1991), suggesting that low inclusion rates of Cd have the ability to affect trace element status. Rogowska et al. (2008) reported that 96 days of Cd administration (10 mg/kg body weight) increased kidney Cd concentrations (1.13 mg/kg) in treated sheep compared with control animals (0.192 mg/kg). Kidney concentrations of Cd were significantly lower in animals treated with a preparation consisted of Ca, P, vitamin E, Mg, Na, Fe, Cu, Zn, Mn, Co, Se, I, Cl, and biotechnological products, thus highlighting the protective effect of mineral status on Cd absorption.

4. Consequences of cadmium exposure

4.1. Cd toxicity

Cd toxicity in farmed ruminants has been described, but only in experimental studies (Powell et al., 1964; Lynch et al., 1976). There are no published reports of naturally occurring Cd toxicity in farmed ruminants. Acute Cd toxicity arises if exposure (being a function of both concentration and duration) exceeds the liver's ability to sequester Cd bound to MT. Experimentally, this is more likely following short exposure to a large dose compared to long exposure to a small dose of Cd (Wilkinson et al., 2003).

Powell et al. (1964) highlighted the short-term effect of high Cd exposure in growing cattle, and Cd toxicity at higher doses, based on experimental administration of Cd to male calves (Holstein and Jersey). At a dose rate of 2560 mg Cd/kg ration, calves did not gain weight, and all four animals had died within 8 weeks. Very severe growth retardation was observed when calves were fed a high dose of Cd (640 mg Cd/kg ration), and one of four calves died after six weeks. In both of these calf groups, animals displayed clinical signs of Cd toxicity that developed over a period of 16 to 64 days. These included an 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. Depressed growth rates were observed in calves administered 160 mg Cd/kg ration (0.73 kg/day) compared with controls (1.04 kg/day). Growth rates were also reduced when calves were fed a diet of 40 mg Cd/kg ration (0.87 compared with 1.04 kg/day for Cd-fed and controls, respectively), however, this was not statistically significant.

At lower dietary Cd concentrations, variable effects from experimental Cd exposure have been reported. In growing ruminants, several authors have highlighted negative effects of Cd on growth rates (Powell et al., 1964; Doyle et al., 1974; Lynch et al., 1976; Masaoka et al., 1989). In a study examining the effect of high concentrations dietary Cd (15 mg Cd/kg bodyweight daily) and/or Pb (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). In work examining the effect of dietary S (10 g S/kg ration) with Cd (3 mg Cd/kg ration) to growing dairy bulls, Masaoka et al. (1989) found that S alone resulted in decreased daily gains by 15%, whereas the combination of S and Cd decreased daily gains by 19%. In a study of adult cows, 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, these cows were only exposed to Cd for a short period of time.

Table 1

The concentration of Cd in livers and kidneys of farmed ruminants from EU member states and non-EU countries, based on recent published literature. Cd concentrations are given in mg/kg wet weight [mean \pm standard deviation (range)].

Country	Animal	Age	Liver Cd	Kidney Cd	Clinical signs	Reference
<i>EU member states</i>						
Belgium	Cattle	1–11.6 y	0.191 \pm 0.136 (0.029–0.642) [Reference area]	1.142 \pm 0.922 (0.093–4.22) [Reference area]	None reported (animals slaughtered for human consumption)	Waegeneers et al. (2009a,b)
		0.6–10.9 y	0.446 \pm 0.473 (0.055–2.655) [Polluted area]	2.862 \pm 3.159 (0.193–15.3) [Polluted area]	None reported (animals slaughtered for human consumption)	
Belgium	Cattle	Galloway cattle >4 y	0.296 \pm 0.0951 (0.0294–1.17) [Unpolluted area] 0.946 \pm 0.200 (0.226–2.65) [Polluted area]	2.76 \pm 0.633 (0.455–7.99) [Unpolluted area] 7.11 \pm 1.47 (2.13–16.2) [Polluted area]	None reported (animals slaughtered for human consumption)	Roggeman et al. (2014)
		Dairy cows >5 y	0.283 \pm 0.0448 (0.0728–0.71) [Unpolluted area] 0.571 \pm 0.0586 (0.0947–1.14) [Polluted area]	2.58 \pm 0.491 (0.605–7.40) [Unpolluted area] 4.86 \pm 0.576 (0.973–12.1) [Polluted area]	None reported (animals slaughtered for human consumption)	
Finland	Cattle		0.061	0.35	None reported (healthy animals slaughtered for human consumption)	Niemi et al. (1991)
	Cattle	Heifers	0.036		None reported (animals slaughtered for human consumption)	Tahvonon and Kumpulainen (1994)
		Cows	0.066		None reported (animals slaughtered for human consumption)	
Ireland	Cattle	18– \geq 60 m		0.734 (0.04–8.63)	None reported (animals slaughtered for human consumption)	Canty et al. (2014)
Netherlands	Cattle	3 m–15 y	0.16 [Control area] ^a 0.35 [Polluted area] ^a	1.66 [Control area] ^b 4.08 [Polluted area] ^b	None reported (animals slaughtered for human consumption)	Spierenburg et al. (1988)
Poland	Bison (free ranging)	1 y	0.09 \pm 0.01 (0.07–0.10)	0.21 \pm 0.03 (0.18–0.25) [*]	None reported (animals killed by hunters)	Włostowski et al. (2006)
		2 y	0.22 \pm 0.1 (0.10–0.35)	0.41 \pm 0.07 (0.35–0.50) [*]	None reported (animals killed by hunters)	
		4–6 y	0.43 \pm 0.03 (0.40–0.48)	1.24 \pm 0.38 (0.86–1.82) [*]	None reported (animals killed by hunters)	
		7–12 y	0.45 \pm 0.08 (0.31–0.58)	2.79 \pm 0.66 (1.95–3.52) [*]	None reported (animals killed by hunters)	
	Domestic cattle	8–12 y	0.2 \pm 0.06 (0.09–0.27)	1.30 \pm 0.47 (0.68–2.0) [*]	None reported (animals slaughtered for human consumption)	
Poland	Cattle	<2 y	0.159 \pm 0.098 (0.06–0.487)	0.425 \pm 0.195 (0.104–0.937)	None reported (animals slaughtered for human consumption)	Zasadowski et al. (1999)
		>2 y	0.263 \pm 0.166 (0.081–0.672)	1.703 \pm 1.106 (0.59–4.275)	None reported (animals slaughtered for human consumption)	
Poland	Cattle		0.12 [arithmetic weighted mean]	0.61 [arithmetic weighted mean]	None reported (healthy animals slaughtered for human consumption)	Falandysz (1993)
Spain	Cattle	6 m–12 m	0.0307 \pm 0.00124	0.161 \pm 0.00703	None reported (animals slaughtered for human consumption)	Miranda et al. (2001)
	Calves (male)	6–10 m	0.00798 [geometric mean] (ND ^c -7.99)	0.0513 [geometric mean] (0.00243–1.302)	None reported (animals slaughtered for human consumption)	López Alonso et al. (2000)
	Calves (female)	6–10 m	0.00756 [geometric mean] (ND ^c -0.812)	0.0579 [geometric mean] (0.0109–0.712)	None reported (animals slaughtered for human consumption)	
	Cows	2–16 y	0.0833 [geometric mean] (0.0234–0.246)	0.388 [geometric mean] (0.110–1.346)	None reported (animals slaughtered for human consumption)	
	Cattle	9–12 m	0.0229 [geometric mean] (0.00643–0.221) [Rural] 0.0296 [geometric mean] (0.00339–0.131) [Industrialised area]	0.0964 [geometric mean] (0.0042–0.545) [Rural area] 0.161 [geometric mean] (0.0235–0.717) [Industrialised area]	Reported healthy	Miranda et al. (2005)
Sweden	Cattle		0.07	0.39	None reported (healthy animals slaughtered for human consumption)	Jorhem et al. (1991)
Slovenia	Cattle	<5 y	0.094	0.373	None reported (animals slaughtered for human consumption)	Doganoc (1996)
<i>Non-EU countries</i>						
Australia	Cattle		0.176	0.65	None reported (animals slaughtered for human consumption)	Langlands et al. (1988)
China	Cattle	2–4 y	0.21 [Control areas] 1.31 [Mildly polluted areas] 2.47 [Highly polluted areas] 3.24 (ND ^c –82.1)	2.15 [Control areas] 6.64 [Mildly polluted areas] 38.3 [Highly polluted areas] 7.92 (0.012–117)	None reported (animals reared in an experimental area)	Cai et al. (2009)
Jamaica	Cattle				None reported (animals slaughtered for human consumption)	Nriagu et al. (2009)
Iran	Cattle	1–10 y	0.0497	0.1371	None reported (healthy animals slaughtered for human consumption)	Rahimi and Rokni (2008)
Morocco	Cattle		1.45 (0.82–2.02) ^a	4.38 (2.42–5.74) ^b	None reported (animals reared in an experimental area)	Sedki et al. (2003)

* Kidney cortex only.

^a 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%.

^b Results converted from dry weight to wet weight by dividing by 2.35, based on the assumption that the water content of a kidney is 70.2%.

^c Not detectable.

For comparison, a range of conditions are reported in people following chronic Cd exposure, including itai-itai disease which is characterised by multiple fractures, bone pain, osteoporosis and osteomalacia in conjunction with renal disease (Noda and Kitagawa, 1990). In people exposed to Cd concentrations of 30–50 µg per day, there is an increased risk of bone fracture, cancer, kidney dysfunction and hypertension (Mendez-Armenta and Rios, 2011).

4.2. Other adverse effects

As outlined in Table 1, no clinical signs have been reported in farmed ruminants presenting with elevated liver or kidney Cd concentrations.

Work conducted in The Netherlands suggest that exposure to low Cd concentrations can adversely affect bovine reproduction (Kreis et al., 1993). In a study comparing the reproductive performance of dairy cows in areas with and without long-term exposure to Cd pollution, a lower twinning rate [odds ratio (OR) = 0.63 (0.47–0.84)] was found, and there were more birth complications, for both calves [OR = 1.50 (1.25–1.80)] and cows [OR = 1.49 (1.24–1.79)]. More inseminations [OR = 1.20 (1.01–1.43)] were needed for conception in the exposed area. Deaths among twins [OR = 1.66 (0.90–3.07)] were not significantly higher. Perinatal death, premature death, age at, or reasons for, slaughter was not consistently different. In the exposed and non-exposed areas, the soil Cd concentrations were 1.0–2.5 and 0.4 mg/kg dry weight, respectively. Further, in an earlier study conducted in the area (Spiereburg et al., 1988), mean kidney Cd concentrations of 9.58 mg/kg dry weight [2.0 mg/kg wet weight, based on conversion suggested by Phillips and Tudoreanu (2011)] and 3.90 mg/kg dry weight [0.82 mg/mg wet weight] were recorded in cattle from the exposed and non-exposed areas, respectively. The authors concluded that long-term exposure to low levels of Cd was associated with impaired reproduction in dairy cows.

Dietary Cd also has an adverse impact on milk production. In an experiment conducted on 3 Holstein cows, large doses of Cd (3 g daily for 2 weeks) led to a decline in milk production and an elevation in the fat content of milk. There was also a reduction in concentrate consumption and weight loss (Miller et al., 1967).

4.3. Threshold concentrations

Daily dietary Cd of greater than 30 mg/kg has resulted in anorexia, decreased growth rates, reduced milk production and abortions (National Research Council, 2001). Cd accumulation in muscle only occurs when daily dietary Cd is at least 30 mg/kg in feed, which are unlikely to occur even in the most polluted regions (Wilkinson et al., 2003). It has been suggested that diets between 5 and 30 mg/kg/day have the potential to affect animal performance by altering absorption of Cu and Zn (National Research Council, 2001). This is consistent with work by Wilkinson et al. (2003) who reported a critical Cd dose in sheep of 2.5 mg/kg body weight/day which over 1 year led to the production of chronic toxicity, including subclinical effects. It is also consistent with a report from the European Food Safety Authority which suggested that clinical signs are unlikely with a daily dietary Cd intake of less than 5 mg/kg feed (European Food Safety Authority, 2004). Nonetheless, adverse effects have inconsistently been observed at lower Cd concentrations. On the one hand, early signs of liver cell degeneration were seen in sheep following consumption of corn silage with a cadmium content of 1.7 mg/kg dry matter (Heffron et al., 1980). In contrast, no signs of toxicity were observed in bulls fed concentrates and maize silage with 1.5–2.0 mg Cd/kg dry matter (Vreman et al., 1988). The minimum toxic level and maximum safe dietary concentrations of Cd have not been fully elucidated, noting that its effects are dependent on trace element status and the interaction between Cd and Zn, Cu, Fe and Ca (Bampidis et al., 2013).

There is also general agreement among authors concerning threshold concentrations for tissue Cd associated with biological effects.

Kidney damage, the most typical feature of chronic Cd intoxication, is generally assumed to occur at kidney Cd concentrations of 80–200 mg/kg wet weight (Shore and Douben, 1994; López Alonso et al., 2000). Similarly, based on wildlife work by Furness (1996) and Law (1996), Fisk et al. (2005) suggests threshold levels of biological effects for Cd of 20–200 and 50–400 mg/kg wet weight in the liver and kidneys, respectively. Generally consistent with these values, Puls (1994) proposed categories of kidney Cd concentrations with respect to animal health: low (0.05–1.5 mg/kg), high (5.0–36 mg/kg) or toxic (100–250 mg/kg). These guidelines must be interpreted with care, noting that Cd concentrations in blood and tissue are known to vary with different types of exposure.

Cd limits are regulated in a number of countries, specifically to protect human rather than animal health. In the European Union, for example, the maximum permitted Cd concentration in complete and complementary feed for ruminants is 1.0 and 0.5 mg/kg, respectively, each at moisture content of 12% (European Commission Directive 2002/32/EC). The maximum Cd concentration in muscle, liver and kidneys of cattle for human consumption are set by European Commission Regulation 1881/2006 (amended by No. 629/2008) at 0.05, 0.5 and 1.0 mg/kg wet weight, respectively.

Considerable work has been conducted seeking to predict kidney Cd concentrations based on intake. Based on a meta-analysis of feeding trials, Prankel et al. (2004) found that Cd concentration in feed and duration of exposure were the primary predictors of kidney Cd concentrations. Other variables including dry matter intake, the vehicle of the elevated Cd in the diet, animal age, weight, and sex were not significant. A model to predict Cd concentrations in sheep liver and kidneys from soil and dietary characteristics has recently been described (Phillips and Tudoreanu, 2011). Using this model with realistic parameter estimates, the predicted kidney Cd concentration of 1 mg/kg would be exceeded following an exposure period of 150 days of grazing plus supplementary feed, given a soil Cd concentration of 1 mg/kg dry weight.

5. Interaction between cadmium and essential trace elements

An improved understanding of the interaction of Cd with other elements may provide the key to understanding the effects of Cd on health. Cd interacts with the metabolism of a number of different trace elements (López Alonso et al., 2004), including Ca, Zn and Fe (Goyer, 1995; Peraza et al., 1998), Cu (Peraza et al., 1998), proteins, and vitamins C and D (National Research Council, 1980). Further, perturbation of Ca, Zn or Fe homeostasis plays a key role in the toxicological action of Cd, leading to a general threat to basic cellular functions (Goyer, 1995; Martelli et al., 2006).

The influence of Cd on Ca concentrations and bone composition in cattle has not been reported in the literature. In humans, the interaction between Ca and Cd is well understood in the context 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). Furthermore, 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 (Brzówska et al., 2011).

Cd is a potent inhibitor of Cu metabolism, exerting a much stronger antagonistic effect in experimental studies (Davies and Campbell, 1977; Hall et al., 1979) than either Mo (Mills et al., 1977) or Zn (Grant-Frost and Underwood, 1958). In sheep, dietary Cd led to a decrease in liver Cu concentrations (Mills and Dalgarno, 1972; Doyle and Pfander, 1975). The adverse effects of Cd exposure can be improved by supplementation with Cu (Bremner and Campbell, 1978). In sheep, increased

dietary Mo (up to 15.45 mg/kg DM) and 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 comparison to these experimental studies, observational studies provide less conclusive evidence of these effects. In several studies, reduced Cu was associated with increased concentrations of Cd (Zasadowski et al., 1999; López Alonso et al., 2002; Sedki et al., 2003; Cai et al., 2009). Further, Nriagu et al. (2009) suggest that high concentrations of kidney Cd in Jamaica may be related to hypocupraemia, in areas where soils are polluted with Cd. However, high tissue Cu concentrations have been reported in animals from both contaminated and non-contaminated sites (Waegeneers et al., 2009a). The work of López Alonso et al. (2002) is of particular interest, with the authors describing a negative correlation between Cd and Cu in cattle grazing in an area of low industrial pollution.

Cd also interacts with Fe, Mn and Mo metabolism, but through mechanisms that are not well understood (López Alonso et al., 2004). Information is lacking on the interaction between Fe and Cd in ruminants. In humans, Fe deficiency during pregnancy is correlated with increased Cd adsorption and body burden (Åkesson et al., 2002), whereas in suckling piglets, Cd uptake was not higher in Fe deficient animals (Öhrvik et al., 2007). An association between Cd and Mn has been described in sheep exposed to high dietary Cd (Doyle and Pfander, 1975), and increased dietary levels of Mo has been shown to reduce Cd accumulation in sheep (Smith and White, 1997).

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 Cd binding from MT to higher weight proteins, thus allowing 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. Tomza-Marciniak et al. (2011) demonstrated the inverse relationship between Se and Cd in cattle in a non-polluted area of Poland, highlighting an association between heavy metals and trace elements, even at low Cd concentrations.

Peraza et al. (1998) suggested that toxicity of Cd may disrupt Zn metabolism. Diets with inadequate Zn may contribute to the development of Cd toxicity at lower Cd exposure. Cd has an inhibitory effect on Zn containing enzymes, including carboxypeptidase and α -mannosidase, and may replace Zn 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).

6. Conclusions

Concerns regarding Cd ultimately relate to human health, with the accumulation of Cd in the agricultural environment increasing the potential for Cd to enter products for human consumption (Roberts et al., 1994). In farmed ruminants, Cd exposure may be associated with a number of different activities, including industrial processing, mining, and agricultural practices, and is also higher in soils in some geographic regions. Cd has the ability to effect changes on a wide spectrum of pathophysiological functions in animals. Although Cd toxicity in farmed ruminants has been demonstrated experimentally, there are no published reports of naturally occurring Cd toxicity in farmed ruminants. Clinical signs of Cd intoxication are unlikely with a daily dietary Cd intake of less than 5 mg/kg feed, which is 5–10 times higher than the maximum permitted Cd concentration in ruminant feed in the European Union. In farmed ruminants, Cd levels in tissue are largely dependent on the Cd content of diet. However, many factors affect Cd availability, relating to soils, plants and the presence of other trace elements including Ca, Cu, Fe, Mn, Mo, Se and Zn. Experimental studies have highlighted the ability of Cd to alter trace element status, and the protective effect of good mineral status, however, there remain

gaps in knowledge of the impact of these interactions on the health and productivity of farmed animals.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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Relevant European legislation

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- Directive 2002/32/EC, 2002. Directive 2002/32/EC of the European Parliament and of the Council of 7 May 2002 on undesirable substances in animal feed. *Off. J. L* 140, 10 (30 May).