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Interactions Between Toxic and Essential Trace Metals in Cattle from a Region with Low Levels of Pollution

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Abstract. Studies on the impacts of pollutant metals and metalloids on livestock have largely focused on animals with relatively high levels of exposure. The impact of low-level environmental contamination, which is more common on agricultural land, is largely unknown. The principal aim of the present study was to examine the effects of low-level environmental contamination on trace metal metabolism in cattle from the rural and relatively uncontaminated region of Galicia (NW Spain). Correlations between toxic (cadmium, lead, and arsenic) and essential trace elements (copper and zinc) were evaluated in the tissues (liver, kidney, and muscle) and blood of 494 cattle from throughout Galicia. Cadmium was the toxic element that had the greatest influence on copper and zinc homeostasis. There was a significant positive association between renal cadmium and zinc residues and a significant negative correlation between kidney cadmium and copper. These interactions are likely to be the result of cadmium-induced effects on metallothionein synthesis. Lead and zinc were positively associated in the kidney, although the mechanism of this interaction is uncertain. Arsenic and copper concentrations were strongly correlated with each other in the liver and may indicate that the high copper levels in animals from copper-rich areas in Galicia interfere with their arsenic excretion. The essential metals copper and zinc were also significantly associated with each other in calves but not in cows.

Industrial and agricultural processes have resulted in the release of many toxic metals into the environment, although relatively high concentrations can also occur naturally. Cadmium, lead, arsenic, and mercury are the elements that have probably caused the most concern. This is because they are readily transferred through food chains and can pose a potential health risk to animals and humans (Friberg *et al.* 1979). Elevated levels of toxic metals and metalloids have been detected in farm animals from industrial areas (Spierenburg *et al.* 1988; Kottferová and Korekénová 1995). At high doses, these elements can be acutely lethal. At lower doses, their effects on domestic livestock include mutagenicity, carcinogenicity, teratogenicity, inmunosuppression, poor body condition, and impaired reproduction (Janicki *et al.* 1987; Bires *at al.* 1995).

The susceptibility of livestock and other animals to toxic metals is affected by various factors. Arguably, one of the most important is the interaction between essential and toxic elements (Goyer 1995), toxicity varying with the trace element metabolic status of the animal. However, trace element metabolism is itself affected by toxic metals. Disturbances in the homeostasis of essential elements may, in fact, be one mechanism of toxicity (Liu *et al.* 1992).

Toxic metal accumulation and the resultant interactions between toxic and trace elements have been investigated in cattle and other farm animals from polluted areas (Koh and Judson 1986; Langlands *et al.* 1988; Spierenburg *et al.* 1988; Telisman *et al.* 1990) and in experimental studies (Reddy *et al.* 1987; Wentink *et al.* 1988; Smith *et al.* 1991a, 1991b). These studies have largely involved exposure of animals to relatively high levels of contaminants that usually occur only in localized areas. The environmental concentrations of toxic elements on most agricultural land are likely to be relatively low. Despite this, there is little information on the effects of low-level pollution on livestock. The aim of the present study was to determine whether low-level uptake of toxic metals resulted in disturbances in essential trace metal metabolism. This was done by quantifying toxic and trace element concentrations in cattle from the rural and largely uncontaminated region of Galicia (NW Spain); cattle are the predominant type of livestock in this area.

Materials and Methods

The data on the concentrations of toxic (cadmium, lead, and arsenic) and essential elements (copper and zinc) in Galician cattle on which the present study is based have been summarized elsewhere (López Alonso *et al.* 2000a). The data are derived from measurements made on a stratified random sample of cattle organs (liver, kidney, and muscle) and blood taken from every slaughterhouse in Galicia during June–November 1996. The age of the animals ranged from 6–10 months (calves) and to 2–16 years (cows). A similar number of male and female calves were sampled, but all adult animals were cows

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(females). Organs were taken from a much larger number of calves (438) than cows (56) because most cattle in Galicia are slaughtered when young (6–10 months old). Full details of the collection of samples, analytical methods, limits of detection, and quality control are given by López Alonso *et al.* (2000a).

Interactions between toxic and trace elements were investigated by correlation analysis. All statistical analyses were run using the Minitab for Windows (v.11) program. Nondetected values were assigned a value of half the limit of detection for statistical purposes. A high proportion of samples had nondetected values for the toxic metals, especially in the muscle and blood (48–90% of all samples), and datasets were not all normally distributed, even after log-transformation. Therefore, the significance of correlations between pairs of elements in each tissue was determined from Spearman rank correlations (R_s).

Statistical analyses that involved copper concentrations in muscle were potentially confounded. This was because pectoral muscle had been sampled from calves and diaphragm from cows; subsequent chemical analysis had revealed that diaphragm contained 1.65 times more copper than pectoral muscle from the same animal (López Alonso *et al.* 2000b). So that data for muscle copper concentration for calves and cows could be analyzed together in the present study, the copper concentrations in pectoral muscle in cows were predicted from their diaphragm copper concentrations. These predicted values for cows were then used in subsequent statistical tests.

Results

The correlations between each pair of elements in the different tissues of all the animals sampled are given in Table 1. Correlations between the various toxic elements and between toxic and essential metals in muscle and blood were generally weak and highly influenced by the very large number of animals that had undetectable levels of cadmium, lead, and/or arsenic (see Figures 1–4). Such correlations are likely to be spurious; indeed, when animals that had nondetected concentrations of these elements were excluded from the analysis, most of these weak correlations disappeared. However, other studies that have reported correlations between tissue metal concentrations have used data for all animals, including those with nondetected values. Therefore we, too, report the results of analyses carried out on all the data (Table 1) but specify when correlations were not statistically significant if only data for animals with detectable toxic metal residues were analyzed. Furthermore, some toxic elements, particularly cadmium, accumulate with age in mammals (Bremner 1979; Friberg *et al.* 1979), including cattle in Galicia (López Alonso *et al.* 2000a). When tissue burdens did vary with age, the associations between metal residues in Galician calves and cows were analyzed separately. Gender had no statistically significant effect on toxic metal residues in Galician calves, apart from kidney cadmium levels, which were higher in females than males (López Alonso *et al.* 2000a). Therefore, analysis of the associations between elements was not carried out separately for males and females apart from for those involving renal cadmium.

The only significant associations between toxic elements were between cadmium and lead. There were positive correlations between the two elements in liver, kidney, muscle, and blood (Figure 1, Table 1). However, only the correlation in the kidney was significant (R_s = 0.129, $p < 0.01$) when the analysis was restricted to animals that contained detectable concentrations of both metals. Kidney residues were significantly higher in cows than calves for both metals (López Alonso *et al.* 2000a) and the strength of the correlation between renal cadmium and lead concentrations was improved when the analysis was carried out only for cows (liver: R_s = 0.290, $p <$ 0.05; kidney: R_s = 0.433, $p < 0.001$). The same correlations in young calves were weak and only statistically significant in the muscle (R_s = 0.212, $p < 0.01$) and blood (R_s = 0.244, $p <$ 0.01). Gender had no significant effect on the interaction between cadmium and lead renal concentrations, there being no significant association between the two metals in either males (R_s = 0.031, $p > 0.05$) or females (R_s = 0.116, $p > 0.05$).

There were a number of statistically significant associations between toxic and essential metals (Table 1), especially between cadmium, copper, and zinc (Figure 2). Cadmium and zinc were positively correlated with each other in the kidney and blood. In contrast, cadmium and copper were negatively correlated in the kidney and muscle but positively associated with each other in blood. The strongest correlations between cadmium and either copper or zinc were in the kidney, the organ that has the greatest storage capacity for cadmium. Those correlations remained statistically significant when animals with nondetectable levels of renal cadmium were eliminated from the analysis and were most marked in cows (cadmium/zinc: R_s = 0.606, $p < 0.001$; cadmium/copper: R_s = −0.498, $p < 0.001$), which generally had higher renal cadmium concentrations than calves. Renal cadmium, zinc, and copper concentrations were still correlated with each other in calves, but the strength of the associations was weaker (cadmium/zinc: R_s = 0.117, $p < 0.05$; cadmium/copper: R_s = −0.162, $p < 0.01$); similar associations occurred when data for male and female calves were analyzed separately although they did not achieve statistical significance, probably because of the reduced sample sizes. In contrast, correlations between cadmium and either of the trace elements in muscle and blood were only weakly significant and highly influenced by animals with nondetectable levels of cadmium. None were statistically significant when only animals with detectable cadmium residues were included in the analysis.

There were also significant positive associations between lead and zinc in the liver, kidney, and muscle (Table 1, Figure 3). However, only the correlation in the kidney was statistically significant when the analysis was restricted to animals with detectable lead residues and this was significant in both cows and calves (calves: R_s = 0.306, $p < 0.001$; cows: R_s = 0.390, $p < 0.001$). There were no significant correlations between lead and copper residues in Galician cattle. The only significant relationship between arsenic and the trace elements was a positive but relatively weak association between arsenic and copper in the liver (Table 1, Figure 4). When the analysis was carried out using only animals that contained detectable levels of arsenic, it was apparent that this association was actually highly significant (R_s = 0.761, $p < 0.001$, Figure 4). Restriction of the analysis in this way did not reveal any other significant relationship between arsenic and copper or zinc.

There were significant positive associations between the essential metals, copper and zinc, in all the tissues and the blood (Table 1, Figure 5). The strength and statistical significance of these interactions varied when data for young and adult animals were analyzed separately. The strength of the associations in all the tissues was improved when only calves

Table 1. Spearman Rank correlation coefficients for the relationships between elements in Galician cattle (n = 494)

	Cadmium	Lead	Arsenic	Copper	Cadmium	Lead	Arsenic	Copper
	liver				kidney			
Lead	0.096*				0.173***			
Arsenic	−0.029	−0.011			0.054	0.080		
Copper	−0.043	−0.011	0.088*		−0.167***	0.019	0.031	
Zinc	0.049	0.138**	0.059	0.129**	0.341***	0.401***	0.060	0.234***
	muscle				blood			
Lead	0.229***				0.120*			
Arsenic	0.000	0.025			0.016	−0.006		
Copper	−0.106*	0.087	0.076		0.188***	−0.005	0.040	
Zinc	0.013	0.155**	0.030	0.375***	0.217***	−0.048	0.006	0.230***

* Significant at $p < 0.05$.
** Significant at $p < 0.01$.
*** Significant at $p < 0.001$.

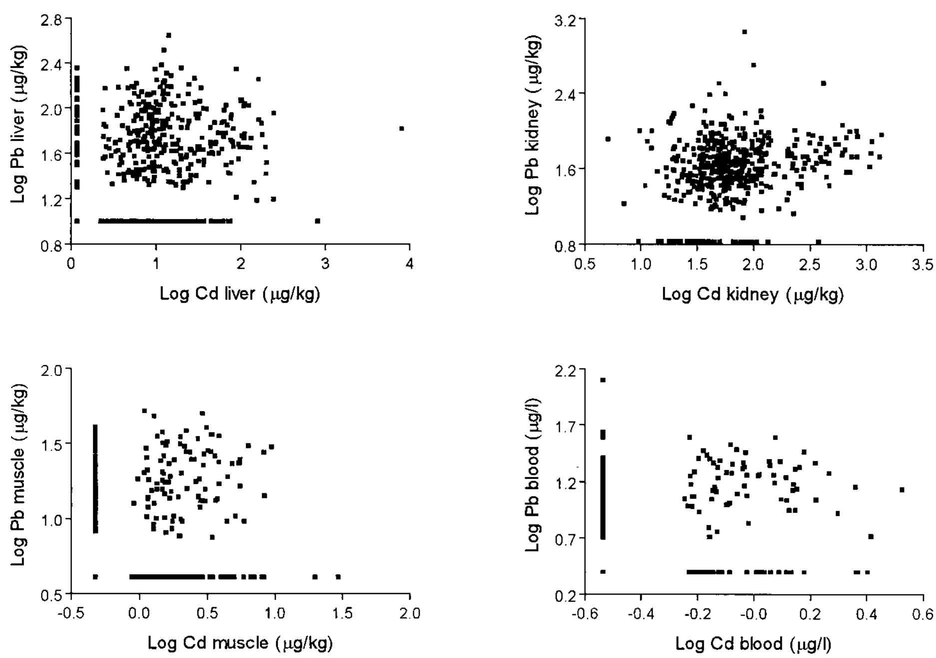

Fig. 1. Scatterplots showing the relationships between concentrations of cadmium (Cd) and lead (Pb) in the liver, kidney, muscle, and blood in Galician cattle

were analyzed (liver: $R_s = 0.161$, $p < 0.01$; kidney: $R_s = 0.450$, $p < 0.01$; muscle: $R_s = 0.310$, $p < 0.01$; blood: $R_s = 0.220$, $p < 0.01$), but zinc and copper residues were not significantly correlated with each other in cows except in muscle ($R_s = 0.398$, $p < 0.01$) and blood ($R_s = 0.312$, $p < 0.01$).

Discussion

The levels of cadmium, lead, and arsenic measured in Galician cattle were low. The tissue and blood residues of these toxic metals and those of zinc were similar to those found in the tissues of cattle from relatively unpolluted rural areas in other countries (López Alonso *et al.* 2000b). However, the liver copper concentrations in Galician cattle were high compared with those in cattle from other agricultural regions. This is because some animals came from areas with naturally or anthropogenically elevated environmental concentrations of copper (López Alonso *et al.* 2000c). Despite the generally low level of pollution in Galicia, there were significant interactions between toxic and essential trace metals in Galician cattle. These associations were broadly similar in pattern to those described in cattle that were from heavily polluted areas or that were experimentally dosed with relatively high levels of toxic metals (Reddy *et al.* 1987; Spierenburg *et al.* 1988; Wentink *et al.* 1988; Smith *et al.* 1991a, 1991b). These interactions have also been observed in other species exposed to relatively high levels of toxic metals (Norheim 1987; Wenzel and Gabrielsen 1995; Teigen *et al.* 1999; Elliot *et al.* 1992). However, as far we are aware, this is the first study to demonstrate such interactions in animals grazing in areas with only background levels of toxic metals.

In Galician cattle, cadmium and lead tissue residues were generally positively correlated with each other, although these associations did not achieve statistical significance in all tis-

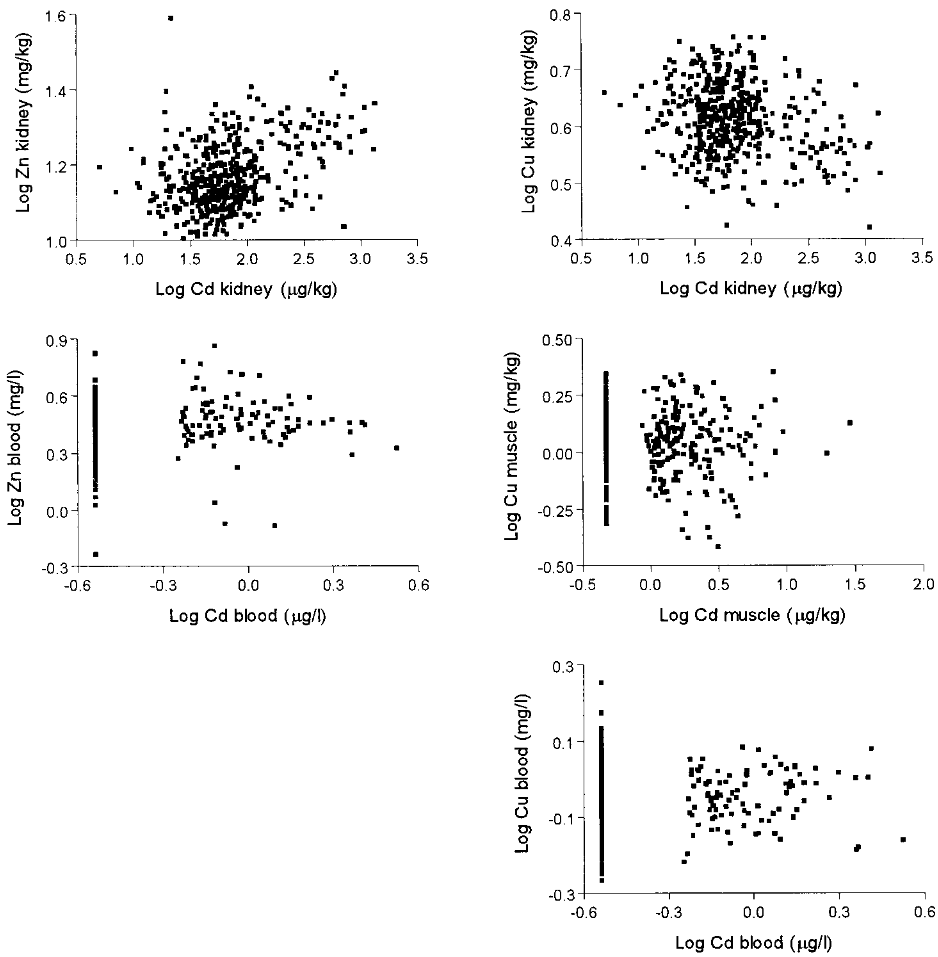

Fig. 2. Scatterplots showing the relationships between concentrations of cadmium (Cd) and the essential metals zinc (Zn) and copper (Cu) in the liver, kidney, muscle, and blood in Galician cattle. Only those relationships that were statistically significant (Table 1) are shown

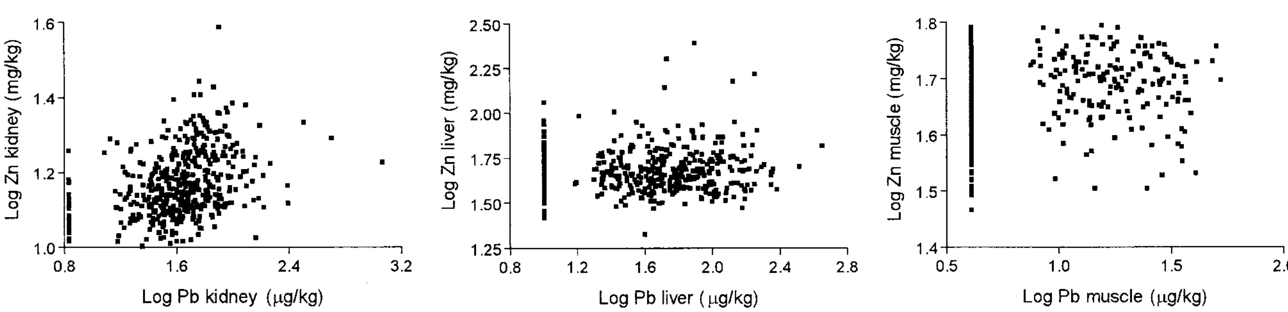

Fig. 3. Scatterplots showing the relationships between concentrations of lead (Pb) and zinc (Zn) in the liver, kidney, and muscle in Galician cattle

sues. Correlations between cadmium and lead residues have also been described in cattle exposed to relatively low environmental concentrations of both metals in agricultural regions of Germany (Kreuzer *et al.* 1978), The Netherlands (Vos *et al.* 1987), and Finland (Tahvonen and Kumpulainen 1994). Such associations can be due to concurrent exposure to different elements or the result of interactions during absorption, metabolism, and excretion. Concurrent exposure could account for the significant association between cadmium and lead in Galician cattle; spatial analysis of cadmium and lead residues in young calves suggests that individuals with higher levels of both metals were from localized areas (López Alonso 1999). However, the fact that these associations were more pronounced in adult animals that had higher tissue burdens than calves could also indicate that other age-related factors affected toxic metal accumulation.

The correlations between toxic and essential trace metals that were detected in Galician cattle may be the result of toxic metals affecting trace element metabolism. Interactions between cadmium, copper, and zinc have been widely reported in mammals from contaminated areas and in experimental animals (Webb 1979; Nicholson *et al.* 1984; Spierenburg *et al.*

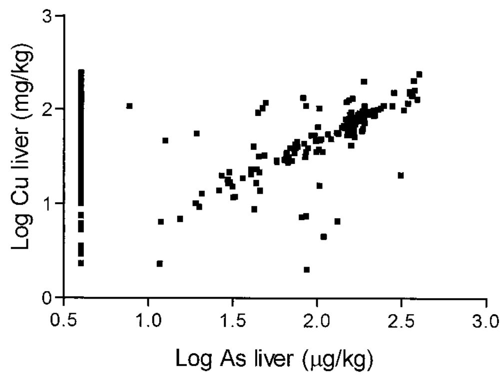

Fig. 4. Scatterplots showing the relationship between liver arsenic (As) and copper (Cu) concentrations in Galician cattle

1988; Wentink *et al.* 1988; Smith *et al.* 1991a, 1991b) and are a consequence of the shared ability of these metals to induce metallothionein (MT) synthesis (Webb 1979). Although it was initially thought that the only function of MTs was to provide a defense against toxic cations (especially cadmium), it is now known that these proteins have a function in regulating normal copper and zinc metabolism and in protecting cells against damage induced by alkylating agents, oxygen radicals, and ionizing radiation (Cherian *et al.* 1994; Baudrimont *et al.* 1999). Other metals, such as lead, mercury, and silver, also induce and bind to MTs, but cadmium has a more marked impact on essential metal homeostasis because of its greater capacity to induce MTs (Gochfeld 1997). The association between cadmium, copper, and zinc in Galician cattle was most pronounced in the kidney. This is the organ that accumulates the highest concentrations of cadmium-MT following low-level chronic exposure (Dudley *et al.* 1985), the type of exposure thought to be most common in the natural environment (Scheuhammer 1987). Cadmium was not associated with copper and zinc in the muscle because cadmium concentrations in this tissue were usually very low and may not have exceeded the thresholds for MT synthesis; thus cadmium would not have been retained in the muscle but transported to the liver (Webb 1979).

In our study, cadmium and zinc were positively associated in the kidney of Galician cattle. An increase in tissue zinc concentration following both acute and chronic exposure to relatively high levels of cadmium has been observed in other species (Nicholson *et al.* 1984; Chmielnicka *et al.* 1989; Elliott *et al.* 1992; Roméo *et al.* 2000) and is the result of cadmium-induced MT induction (Chmielnicka *et al.* 1989). Zinc, as well as cadmium, is sequestered by the induced MT, and the increase in tissues zinc concentration is proportional to the amount of cadmium present in the tissue (Nicholson *et al.* 1984).

In contrast to zinc, copper was negatively correlated with cadmium in the kidney of Galician cattle. Experimental studies have demonstrated that cadmium and copper compete for the cation-binding thiol sides of MT, and copper can be displaced by cadmium (Wentink *et al.* 1988). Although the affinity of copper for the thiol sites is generally greater than that of cadmium (Funk *et al.* 1987; Cosson 1994; Baudrimont *et al.* 1999), and so displacement of copper by cadmium might not be expected, MTs induced by cadmium have a less specific binding capacity for copper than that for cadmium (Foulkes 1993). Binding capacity is also related to the relative concentrations of each metal in the cell; relatively high cadmium to copper ratios facilitate displacement of copper (Cosson 1994). Given this, it was surprising that there was not also a significant negative relationship between copper and cadmium in the livers of Galician cattle. Negative associations between liver cadmium and copper have been observed in cattle and sheep that were experimentally dosed with cadmium or were from cadmium-contaminated areas (Koh and Judson 1986; Wentink *et al.* 1988; Smith *et al.* 1991a, 1991b; Miranda 1999), and copper deficiency has been reported in cattle from areas with high cadmium pollution (Koh and Judson 1986; Spierenburg *et al.* 1988; Wentink *et al.* 1988). The lack of interaction between liver cadmium and copper in the present study may have been a result of the high copper levels that occur in Galician cattle (López Alonso *et al.* 2000a) and the overall relatively low level of cadmium contamination. The liver is the major organ of copper accumulation, and copper that is neither required for normal hepatocyte metabolism (incorporated into cupro-enzymes) nor incorporated into ceruloplasmin (for transport to extra-hepatic tissues) is sequestred by MT (Harrison and Dameron 1999). Animals with high liver copper levels would have had relatively low liver cadmium:copper ratios, which would have limited any cadmium-induced displacement of copper from MT.

Because correlations are not proof of causation, it cannot be firmly concluded from the results of the present study that the low levels of cadmium accumulated by Galician cattle caused an alteration in zinc and copper homeostasis. It is also possible that zinc and copper, in fact, actually determined the amount of cadmium accumulated, or other factors influenced the tissue concentrations of all three metals. However, the associations between cadmium, copper, and zinc occurred in both calves and cows; were stronger in cows (which had higher renal cadmium concentrations, reflecting the age-related nature of cadmium accumulation); and, most important, were similar to interactions observed in animals experimentally dosed with cadmium. Thus, the observed relationships between cadmium and both copper and zinc residues in Galician cattle were consistent with what would be expected from current knowledge of the mechanisms of cadmium toxicity and suggest that cadmium-mediated effects on trace element metabolism occur even at low levels of environmental exposure.

There were two other significant associations between toxic and trace elements in Galician cattle, one between lead and zinc, the other between arsenic and copper. Interactions between lead and zinc are not as well defined as those between lead and either calcium or iron. In our study, lead and zinc residues were strongly correlated with each other in the kidney. Spierenburg *et al.* (1988) described a similar association in cattle from close to zinc refineries and also in animals from an uncontaminated site. Experimental studies have shown that zinc excretion is elevated in lead-exposed animals and zinc deficiency enhances lead absorption (Goyer 1995, 1997), although the mechanisms for these various interactions are not understood. Liver arsenic and copper were strongly correlated in Galician cattle that had been exposed to arsenic. Interactions between tissue arsenic

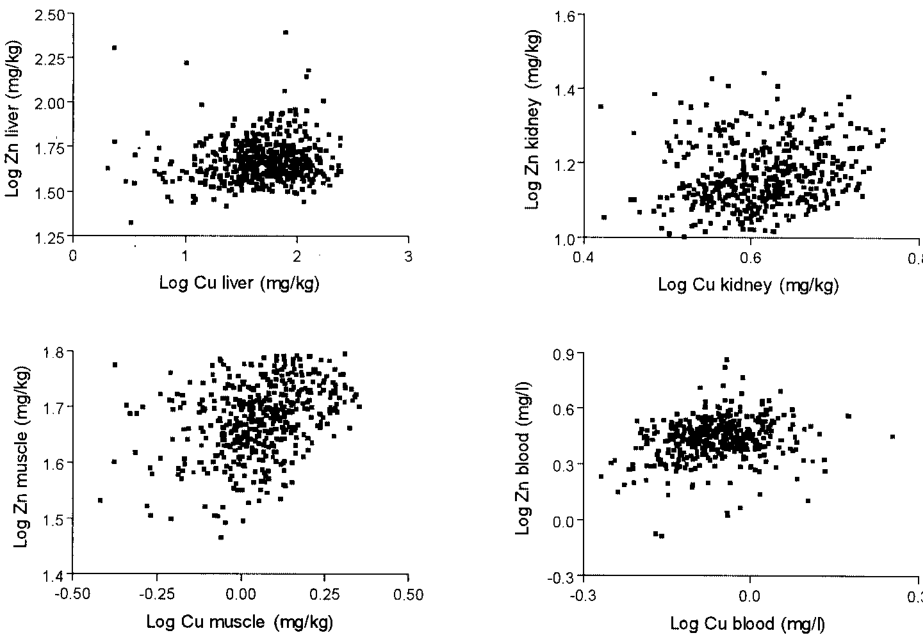

Fig. 5. Scatterplots showing the relationships between copper (Cu) and zinc (Zn) concentrations in the liver, kidney, muscle, and blood in Galician cattle

and copper have only been described previously in rat and guinea pig kidney (Schmolke *et al.* 1992; Hunder *et al.* 1999; Ademuyiwa and Elsenhans 2000); oral administration of inorganic arsenic led to copper accumulation in the kidney, but not in the liver or red blood cells, where arsenic is also accumulated (Ademuyiwa and Elsenhans 2000). The characteristics and mechanisms of renal-specific copper accumulation are unknown but are thought to be due to renal rather than hepatic or biliary processes as liver copper levels are unaffected (Schmolke *et al.* 1992; Ademuyiwa and Elsenhans 2000). In contrast, arsenic and copper were only correlated in the liver in Galician cattle, suggesting that there is another mechanism of interaction in ruminants. This could involve the selenium-dependent glutathione peroxidase enzyme (GSH-Px) which plays a role in arsenic methylation and excretion. High copper intakes reduce intestinal absorption of selenium in ruminants because highly insoluble copper selenide compounds are formed in the rumen (Koenig *et al.* 1991). If high copper intakes in some Galician cattle reduce the levels of selenium-dependent GSH-Px, those animals would have a reduced capacity to methylate and excrete arsenic, and both their copper and arsenic tissue concentrations would be elevated. Any such association would probably only be apparent in the liver because it is the main storage organ for copper in cattle, whereas kidney copper levels are low and vary little. Though it is also possible that the observed correlation between liver arsenic and copper residues was due to a common source of exposure to both elements, this seems unlikely because the levels of copper and arsenic in calves were correlated with those in soil and there is a negative association between arsenic and copper concentrations in Galician soil ($R_s = -0.268$, $p < 0.01$; López Alonso 1999). However, measurement of selenium and GSH-Px levels is needed to confirm that the high levels of copper in Galician cattle do interfere with arsenic excretion.

The present study also demonstrated that there were significant, positive associations between the essential trace elements themselves, but only in calves. Copper and zinc are both essential components of numerous proteins and enzymes and tissue concentrations are normally under tight homeostatic control, MTs playing an essential role in this homeostasis (Garrett *et al.* 1998). Therefore, it is not surprising that copper and zinc residues were correlated with each other in Galician calves. However, other metals (particularly cadmium) bind to and induce the synthesis of MTs and can disrupt trace element metabolism, thereby altering the normal copper:zinc ratios in body organs that sequester MT. Because cadmium is progressively accumulated with age, any disruption to copper:zinc ratios is most likely to be apparent in older animals, as was the case in Galician cattle.

Conclusion

Although exposure to and accumulation of toxic elements in Galician cattle were well below those generally considered to be toxic, it is likely from the results of the present study that they disturbed trace element metabolism to some extent. The severity of this disruption was unlikely to be sufficient to cause pathological effects by itself. For instance, there was no clinical sign of copper deficiency in animals, even in cows that had the highest levels of hepatic cadmium and the lowest copper concentrations (López Alonso *et al.* 2000a). However, disruption of trace element metabolism by relatively low levels of toxic metals could contribute to the pathogenicity of other metabolic disorders, and lead to a higher susceptibility to disease and a decrease in productivity. The significance of low-level pollution on cattle (and other livestock) production warrants further investigation.

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