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Low ambient temperature decreases cadmium accumulation in the liver and kidneys of the bank vole (*Clethrionomys glareolus*)

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The importance of photoperiod and ambient temperature on the accumulation of cadmium in the liver and kidneys of bank voles was determined in the present study. Males and females, aged 1 month, were given 3.0 μg Cd ml^{-1} drinking water and divided into four groups according to photoperiod (16 h light/8 h dark and 8 h light/16 h dark) and ambient temperature (20 or 5°C); liver and kidneys were removed for cadmium as well as copper, iron and zinc analyses at the end of 6 weeks. Bank voles exposed to 5°C in both photoperiods consumed approximately 30% less water containing cadmium than those kept at 20°C. However, the total accumulation of cadmium in the liver and kidneys of males and females exposed to the low temperatures was 4.3-4.8 and 2.2-3.3 times less than that in animals maintained at room temperature in the long and short photoperiod, respectively. Simultaneously, the low temperature brought about an increase in the copper concentrations in the liver (12-43%) and kidneys (47-78%), giving rise to an inverse correlation between the cadmium accumulation and the tissue copper concentration. In contrast to cadmium and copper, the concentrations of iron and zinc were affected primarily by photoperiod. These findings indicate that ambient temperature is an important determinant of cadmium retention in the bank vole. It appears that low temperature decreases tissue cadmium accumulation not only by reducing cadmium intake but also through changes in copper metabolism.

Keywords: cadmium, copper, iron, photoperiod, temperature, zinc

Introduction

Cadmium is a heavy metal that is commonly considered to be a toxic element for humans and animals (Chmielnicka & Cherian 1986). It is well known that most of the absorbed cadmium after oral exposure is found mainly in the liver and kidneys (Schenkel 1994). There is also considerable experimental evidence that its accumulation in the organs is primarily dose- and time-dependent (Kotsonis & Klaassen 1978). In addition, the tissue concentration of cadmium can be modulated by several other factors such as: dietary copper, zinc, iron, calcium and protein (Flanagan *et al.* 1978, Revis 1981, Jacobs *et al.* 1983, Foulkes 1985, Nordberg *et al.* 1985, Elsehans *et al.* 1987, Felley-Bosco & Diezi 1992), the chemical form in which cadmium occurs in the diet (Groten *et al.* 1991a), and strain, sex and age of animals (Rummler *et al.* 1989, Shaikh *et al.* 1993).

A previous work from our laboratory (Włostowski 1992) has demonstrated that cadmium concentrations in the liver of free-living rodents, the bank vole, captured in spring and summer are 20 to 50-fold greater than those in animals caught in winter, despite the fact that cadmium levels in food (stomach contents) remain generally constant (1.5 μg g^{-1} dry weight) over a year. Thus, the reasons for these dramatic differences are unclear. As photoperiod and ambient temperature in winter and spring or summer in the temperate zone are distinctly different, and bank voles are sensitive to changes in daylength (Tahka 1978), it cannot be ruled out that these two environmental factors may affect, in some way, tissue cadmium accumulation in these animals.

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Therefore, the main purpose of the present work was to examine in laboratory conditions the effect of day length and ambient temperature on cadmium accumulation in the liver and kidneys of bank voles. Since there are several reports which indicate that copper, zinc and iron status can affect the retention of cadmium (Fox *et al.* 1984, Leon & Johnson 1985, Panemangalore 1993, Rimbach *et al.* 1995), the concentrations of copper, iron and zinc in both organs were also determined to establish a relationship, if any, between the tissue status of these elements and cadmium accumulation.

Materials and methods

Animals and experimental design

Bank voles from our own laboratory stock were used throughout the study. One-month-old males and females, weighing 9–11 g, were randomly allocated into four groups according to photoperiod (16 or 8 h) and ambient temperature (20 ± 1 or 5 ± 1°C) at 60–70% relative humidity: (1) 16 h light/8 h dark, 20°C; (2) 16 h light/8 h dark, 5°C; (3) 8 h light/16 h dark, 20°C; and (4) 8 h light/16 h dark, 5°C. Males and females were housed separately in groups of four or five in stainless-steel cages fitted with a plastic floor and a wire-mesh front and top. The cages ($40 \times 25 \times 15$ cm) were divided into the nesting part ($10 \times 25 \times 15$ cm) with hay as a bedding material, and the running compartment (Buchalczyk 1970). For 6 weeks, bank voles received *ad libitum* distilled water (control) or water containing 3.0 μg Cd ml^{-1} and wheat grains which are considered to be an adequate quality food for the bank vole (Meese 1971, Sawicka-Kapusta *et al.* 1987). The food contained (by AAS analysis) 35–42 μg Zn g^{-1}, 5–7 μg Cu g^{-1}, 150–170 μg Fe g^{-1} and less than 0.1 μg Cd g^{-1} (dry weight). In addition, an identical amount of carrot containing less than 0.1 μg Cd g^{-1} dry weight was offered to all animals (1 g $vole^{-1}$ $week^{-1}$) which ate it completely. Water and food intakes were measured weekly.

Trace element analysis

At the end of the 6 week experimental period, bank voles were weighed and anesthetized with dietyl ether, and the liver and both kidneys were removed. The organs were dried to a constant weight at 100°C. A portion of the liver (about 150 mg) and both kidneys were then placed in calibrated glass tubes with 1.5 ml of concentrated nitric acid. After 20 h of sample digestion at room temperature, 0.5 ml of 72% perchloric and 0.1 ml of concentrated sulfuric acids were added and the mixture was heated at 100°C (1 h), then at 150°C (1 h) and finally at 200°C (1 h) (Włostowski *et al.* 1988). The residue, after digestion (about 0.3 ml), was made up with double-distilled water to 5.0 ml (first solution). A portion of the first solution (200 μl) was evaporated to dryness in a quartz crucible at 130°C and the residue was redissolved in an appropriate amount of 0.015 N HNO_3 (second solution). Cadmium analyses of these solutions were carried out by electrothermal atomic absorption spectrophotometry using AAS 3 Carl Zeiss Jena instrument with an EA 3 furnace attachment. The conditions were as follows: wavelength 228.8 nm, drying at 110°C for 15 s, ashing at 250°C for 5 s and atomizing at 1200°C for 5 s. The concentrations of copper, iron and zinc of the first solutions were determined by atomic absorption spectrophotometry in an air–acetylene flame. Aldrich standard solutions and 0.015 N HNO_3 were used to prepare the standard curves. Quality assurance procedures included the analysis of reagent blanks and appropriate standard reference materials [(National Institute of Standards and Technology, Gaithersburg, MD), bovine liver (1577b) and CL-1 cabbage leaves (AGH, Poland)]. The recoveries of cadmium, copper, iron and zinc by this method amounted to 90–95%.

Statistical analysis

Data were expressed as means ± SD. The effect of photoperiod, temperature, sex and their interactions were determined by a $2 \times 2 \times 2$ analysis of variance (ANOVA). The least significant difference (LSD) test was applied when appropriate. Differences at $P < 0.05$ were considered statistically significant. A relationship between cadmium accumulation in the liver and kidneys and the tissue concentrations of copper, iron and zinc was evaluated by using the simple regression analysis. All statistical analyses were performed on log-transformed data.

Results

Bank voles receiving water containing 3.0 μg Cd ml^{-1} showed no significant differences in water and food consumption, final body and organ weights as well as tissue concentrations of copper, iron and zinc as compared with the control animals. The concentrations of cadmium in the liver and kidneys of all control voles did not exceed 0.1 μg g^{-1} dry weight. Therefore, to simplify presentation of the data only bank voles receiving cadmium were taken into further analysis.

During the 6 week experimental period, there were no significant differences in water (cadmium) intake between males and females. A bank vole exposed to 5°C in both photoperiods (16 h light/8 h dark and 8 h light/16 h dark) consumed on average 145 ± 10 ml, whereas that kept in 20°C consumed 185 ± 12 ml 6 $weeks^{-1}$, respectively. Therefore, the total cadmium intake was approximately 435 and 555μg 6 $weeks^{-1}$, respectively. In contrast, the ambient

Table 1. Effect of photoperiod, ambient temperature and sex on body and organ weights of bank voles

Group	Sex	(*n*)	Body weight (g)	Liver dry weight (mg)	Kidneys dry weight (mg)
16 h light/8 h dark					
20°C	male	(13)	19.8 ± 3.0^{a}	289 ± 56^{c}	52 ± 7^{d}
5°C	male	(14)	20.4 ± 2.2^{a}	298 ± 44^{c}	56 ± 6^{d}
20°C	female	(14)	14.2 ± 1.0^{b}	213 ± 23^{b}	$37 \pm 3^{b,c}$
5°C	female	(10)	14.6 ± 4.0^{b}	215 ± 68^{b}	42 ± 7^{c}
8 h light/16h dark					
20°C	male	(15)	13.1 ± 1.9^{b}	$178 \pm 49^{a,b}$	$34 \pm 3^{a,b}$
5°C	male	(14)	13.6 ± 1.2^{b}	$186 \pm 21^{a,b}$	$38 \pm 3^{b,c}$
20°C	female	(13)	12.5 ± 2.0^{b}	166 ± 23^{a}	$32 \pm 3^{a,b}$
5°C	female	(14)	13.1 ± 1.7^{b}	$186 \pm 22^{a,b}$	$37 \pm 4^{b,c}$
Source of variation			Analysis of variance, *P* value		
Photoperiod (P)			0.0000	0.0000	0.0000
Temperature (T)			NS	0.0163	0.0240
Sex (S)			0.0000	0.0000	0.0000
P × T			NS	NS	NS
P × S			0.0000	0.0001	0.0000
T × S			NS	NS	NS
P × T × S			NS	NS	NS

Data are means + SD. All voles received water containing cadmium (3.0 μg ml^{-1}) for 6 weeks. Means in the same column marked with a different superscript letter are ($P < 0.05$) significantly different. NS, not significant.

Table 2. Effect of photoperiod, ambient temperature and sex on the concentrations and contents of cadmium in the liver and kidneys of bank voles

Group	Sex	(*n*)	Liver		Kidneys	
			μg g^{-1} dry wt	μg organ^{-1}	μg g^{-1} dry wt	μg organ^{-1}
16 h light/8 h dark						
20°C	male	(13)	0.96 ± 0.38^{a}	0.27 ± 0.10^{a}	$2.48 \pm 0.48^{a,d}$	0.13 ± 0.03^{a}
5°C	male	(14)	0.22 ± 0.12^{b}	0.06 ± 0.05^{b}	0.53 ± 0.10^{b}	0.03 ± 0.02^{b}
20°C	female	(14)	1.40 ± 0.30^{c}	0.29 ± 0.10^{a}	3.80 ± 1.52^{c}	0.14 ± 0.05^{a}
5°C	female	(10)	$0.30 \pm 0.20^{b,d}$	0.06 ± 0.05^{b}	$0.77 \pm 0.37^{b,e}$	0.03 ± 0.01^{b}
8 h light/16 h dark						
20°C	male	(15)	1.27 ± 0.34^{c}	0.23 ± 0.07^{a}	2.15 ± 0.46^{d}	0.08 ± 0.03^{c}
5°C	male	(14)	0.40 ± 0.20^{d}	0.07 ± 0.05^{b}	0.95 ± 0.20^{e}	0.03 ± 0.02^{b}
20°C	female	(13)	$1.13 \pm 0.33^{a,c}$	0.20 ± 0.07^{a}	3.19 ± 1.22^{f}	0.10 ± 0.03^{c}
5°C	female	(14)	$0.35 \pm 0.18^{b,d}$	0.06 ± 0.03^{b}	1.06 ± 0.32^{e}	0.04 ± 0.02^{b}
Source of variation			Analysis of variance, *P* value			
Photoperiod (P)			0.0074	NS	0.0080	0.0009
Temperature (T)			0.0000	0.0000	0.0000	0.0000
Sex (S)			0.0085	NS	0.0073	NS
P × T			NS	NS	NS	0.0217
P × S			NS	NS	NS	NS
T × S			NS	NS	0.0391	NS
P × T × S			NS	NS	NS	NS

Data are means ± SD. All voles received water containing cadmium (3.0 μg ml^{-1}) for 6 weeks. Means in the same column marked with a different superscript letter are ($P < 0.05$) significantly different. NS, not significant.

Table 3. Effect of photoperiod, ambient temperature and sex on the concentrations of copper, iron and zinc in the liver and kidneys of bank voles

Group	Sex	(*n*)	Copper		Iron		Zinc	
			Liver	Kidneys	Liver	Kidneys	Liver	Kidneys
16 h light/8 h dark								
20°C	male	(13)	24.9 ± 7.0^{a}	23.3 ± 5.0^{a}	711 ± 150^{a}	366 ± 69^{a}	115 ± 17^{a}	153 ± 18^{a}
5°C	male	(14)	35.6 ± 8.0^{c}	34.3 ± 4.7^{b}	727 ± 218^{a}	372 ± 97^{a}	113 ± 14^{a}	149 ± 18^{a}
20°C	female	(14)	23.9 ± 6.0^{a}	24.3 ± 3.1^{a}	1190 ± 460^{b}	641 ± 180^{b}	87 ± 14^{b}	165 ± 15^{a}
5°C	female	(10)	$34.5 \pm 4.0^{b,c}$	35.5 ± 5.0^{b}	1280 ± 380^{b}	596 ± 120^{b}	78 ± 20^{b}	147 ± 13^{a}
8 h light/16h dark								
20°C	male	(15)	$28.3 \pm 6.0^{a,b}$	$28.7 \pm 10.0^{a,b}$	974 ± 240^{b}	631 ± 65^{b}	82 ± 13^{b}	166 ± 22^{a}
5°C	male	(14)	$31.8 \pm 5.3^{b,c}$	43.5 ± 12.0^{c}	985 ± 248^{b}	594 ± 78^{b}	81 ± 13^{b}	155 ± 10^{a}
20°C	female	(13)	$28.4 \pm 6.8^{a,b}$	26.4 ± 7.8^{a}	1210 ± 314^{b}	550 ± 150^{b}	82 ± 8^{b}	165 ± 17^{a}
5°C	female	(14)	35.6 ± 7.9^{c}	47.2 ± 15.0^{c}	1130 ± 260^{b}	600 ± 80^{b}	86 ± 9^{b}	158 ± 24^{a}
Source of variation			Analysis of variance, *P* value					
Photoperiod (P)			NS	0.0027	0.0148	0.0108	0.0001	NS
Temperature (T)			0.0000	0.0000	NS	NS	NS	NS
Sex (S)			NS	NS	0.0000	0.0034	0.0004	NS
P × T			NS	0.0303	NS	NS	NS	NS
P × S			NS	NS	0.0249	0.0006	0.0001	NS
T × S			NS	NS	NS	NS	NS	NS
P × T × S			NS	NS	NS	NS	NS	NS

Data are means ($\mu g\ g^{-1}$ of dry wt) ± SD. All voles received water containing cadmium (3.0 $\mu g\ ml^{-1}$) for 6 weeks. Means in the same column marked with a different superscript letter are ($P < 0.05$) significantly different. NS, not significant.

temperature did not affect food consumption by these animals. The food intake in males from the long photoperiod group (16 h light/8 h dark) amounted to 117.7 ± 8 g (at 5°C) and 115.2 ± 6 g $vole^{-1}$ 6 $weeks^{-1}$ (at 20°C) and was about 115% that of the remaining voles.

As can be seen from Table 1, the final body, liver and kidneys weights were affected primarily by photoperiod, sex and their interaction. Males exposed to the long photoperiod were 26–38% heavier than females kept under the same conditions, and males and females from the short photoperiod group (8 h light/16 h dark). In consequence, the highest absolute weights of liver and kidneys were also recorded in males from the long photoperiod group.

The cadmium levels of the organs are presented in Table 2. Due to significant differences in the absolute weight of the liver and kidneys, the data were expressed as micrograms per gram of dry weight (concentration) and micrograms per organ (content). The concentrations of cadmium in the liver were affected significantly by temperature, photoperiod and sex, while the content was influenced only by temperature. In the long photoperiod group, the concentrations and contents of cadmium in the liver of males and females exposed to 20°C were 4.4 to 4.8-fold greater than those in voles kept at 5°C. In the short photoperiod group, the ratio amounted to 3.1–3.3. The concentrations of cadmium in the kidneys were affected significantly by ambient temperature, photoperiod, sex and temperature × sex interaction, whereas the content of cadmium in both kidneys was affected by temperature, photoperiod and their interaction. The levels of cadmium in the kidneys of males and females from the long photoperiod group exposed to 20°C were 4.4–4.9 times as much as those in voles maintained at 5°C; this ratio reached 2.1–3.0 in the short photoperiod group. The lower ratios observed in the short photoperiod group were primarily due to decreased accumulation of cadmium in the kidneys (significant) and liver (not significant) of bank voles kept at 20°C as compared with the respective long-day animals.

The retentions of copper, iron and zinc in the organs are presented in Table 3. The concentrations of copper in the liver were affected significantly by temperature, whereas in the kidneys by temperature, photoperiod and their interaction. In general, copper concentrations in the liver and kidneys of all bank voles exposed to 5°C were 12 43 and 47–78%,

Table 4. Relationship of total cadmium accumulation by the liver and kidneys to hepatic or renal concentrations of copper, iron and zinc in bank voles ($n = 100$)

Comparison	Regression equation	Coefficient of correlation	P value
Liver Cd content versus hepatic Cu	log Cd = 1.8 – 1.3 log Cu	–0.45	0.0013
Kidney Cd content versus renal Cu	log Cd = 1.6 – 1.3 log Cu	–0.60	0.0006
Liver Cd content versus hepatic Fe	log Cd = –2.0 – 0.03 log Fe	–0.02	NS
Kidney Cd content versus renal Fe	log Cd = –2.6 – 0.02 log Fe	–0.008	NS
Liver Cd content versus hepatic Zn	log Cd = 2.6 + 0.07 log Zn	+0.01	NS
Kidney Cd content versus renal Zn	log Cd = –4.7 + 0.36 log Zn	+0.04	NS

respectively, higher than those in animals kept at 20°C. In the short-day voles kept at 5°C, the renal copper increased significantly as compared with the respective long-day animals. In contrast to copper, the iron concentrations in the liver and kidneys were affected significantly by sex, photoperiod and their interaction. Iron levels in the organs of all long-day males were significantly lower than those in the remaining voles. The concentrations of zinc in the liver were also affected significantly by photoperiod, sex and their interaction. Regardless of temperature, the hepatic zinc in the long-day males was significantly higher than that in the other males and females. Renal zinc was unaffected by photoperiod, temperature and sex.

The regression analysis showed (Table 4) that among the trace elements studied only the copper concentrations appeared to be inversely correlated with the total cadmium content in the liver and kidneys of bank voles.

Discussion

The present work demonstrated the importance of the ambient temperature in the accumulation of cadmium by the liver and kidneys in the bank vole. Both the male and female voles exposed to a low temperature (5°C) in a long and short photoperiod had 2.3 to 4.8-fold less cadmium in the organs than voles kept at room temperature (20°C) (Table 2). Several factors such as decreased intake and absorption, increased excretion and/or antagonistic interactions between cadmium and some essential trace elements could account for the effect of low temperature on the tissue levels of cadmium. Indeed, cadmium intake in voles exposed to 5°C was significantly lower (about 30%) than that in voles maintained at 20°C, which could contribute essentially to a lower retention of cadmium in the former group of animals. However, the difference in cadmium intake was probably too small to bring about over 4-fold differences in the tissue levels of cadmium. It is also unlikely that the low temperature enhanced the excretion of cadmium; the idea is supported by Sawicka-Kapusta *et al.* (1987) who have not found any significant effect of temperature on the rate of cadmium elimination from the bank vole body.

Human and animal studies have demonstrated that the accumulation of cadmium in the liver and kidneys can be modulated by essential metals, particularly copper, iron and zinc (Bremner & Campbel 1980, Fox *et al.* 1984, Chmielnicka & Cherian 1986, Groten *et al.* 1991b, Panemangalore 1993). Those studies emphasize the role of adequate or high copper, iron and zinc status in decreasing the retention of cadmium in the tissues, and are supported by our observations, especially those concerning the relations between cadmium and copper. For instance, Panemangalore (1993) found that copper-adequate rats receiving water containing 5.0 μg Cd ml^{-1} for 12 weeks accumulated 4-fold less cadmium in their livers and kidneys than rats exhibiting a low tissue copper status, i.e. 60 and 45% that of the normal copper concentrations in the liver and kidneys, respectively. Our voles exposed to the low ambient temperature had 12–43 and 47–78% more copper in the liver and kidneys, respectively, than voles kept at room temperature (Table 3). Furthermore, there was an inverse correlation between the cadmium content and copper concentrations in both organs (Table 4). Thus it is reasonable to conclude that copper ions could inhibit, at least to some degree, the accumulation of cadmium in the tissues of bank voles kept at low temperature.

However, the main location and mechanism of this inhibition remain to be established. At the moment at least one point should be stressed; in contrast to most studies carried out so far, the tissue copper changes observed in this work were not due to changes in copper intake. Rather, the changes in copper concentrations might reflect a response of

the bank vole body to cold and thus were regulated by metabolic processes. It is noteworthy that an elevation of hepatic copper in free-ranging bank voles and common shrews caught in cold months has also been observed (Hyvärinen 1972, Włostowski *et al.* 1988). Nevertheless, further studies are required to examine this aspect of copper metabolism in more detail.

Although the precise mechanism by which low ambient temperature decreases cadmium retention in bank voles remains to be determined, one may conclude that this environmental factor could be responsible, at least to some extent, for dramatic seasonal changes in the liver cadmium accumulation observed by Włostowski (1992). It cannot be excluded, however, that other, particularly dietary, factors could also account for the different accumulation of cadmium in the liver of bank voles during winter and spring or summer. For example, calcium and protein have been shown to affect the tissue concentration of cadmium (Washko & Cousins 1977, Revis 1981, Felley-Bosco & Diezi 1992); both dietary calcium restriction and high dietary protein enhance cadmium intestinal absorption and tissue accumulation. Since the content of calcium in the bank vole's food in winter is higher and dietary protein lower than those in spring (Włostowski *et al.* 1988), it is possible that these two factors could also contribute significantly to a lower accumulation of cadmium in the liver of bank voles during winter. In addition, one may speculate that a different chemical form, if any, in which cadmium occurs in the vole's food in particular seasons could have an important effect on tissue cadmium retention. The speculation is based on a previous work (Groten *et al.* 1991a) which demonstrated that rats fed cadmium bound to the protein metallothionein consistently showed less total accumulation of cadmium in the liver (2-fold) and kidneys (1.5-fold) than rats fed the same amount of cadmium but in the form of $CdCl_2$. It should be noted, however, that after exposure to dietary cadmium-metallothionein the ratio of kidney to liver concentrations of cadmium was higher than after $CdCl_2$. Furthermore, frequent observations indicate that there is a gradual redistribution of cadmium from the liver to the kidneys, which may result in a decrease of liver cadmium concentration (Nordberg *et al.* 1985). Thus it is reasonable to assume that not only low ambient temperature but also several other factors could diminish the accumulation of cadmium in the liver of free-living bank voles during winter.

In conclusion, the results of this study emphasize the role of low ambient temperature in decreasing the retention of cadmium in the liver and kidneys of bank voles receiving low levels of cadmium in their drinking water. A question arises, however, whether or not a low ambient temperature also affects tissue cadmium accumulation in the animals exposed to high levels of dietary cadmium. To obtain an answer to this question would be important, especially from a toxicological point of view.

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References

Bremner I, Campbel JK. 1980 The influence of dietary copper intake on toxicity of cadmium. *Annu NY Acad Sci* **355**, 319–332.

Buchalczyk A. 1970 Reproduction, mortality and longevity of the bank vole under laboratory conditions. *Acta Theriol* **15**, 153–176.

Chmielnicka J, Cherian GM. 1986 Environmental exposure to cadmium and factors affecting trace element metabolism and metal toxicity. *Biol Trace Elem Res* **10**, 243–262.

Elsehans B, Schmolke G, Kolb K, Stokes J, Forth W. 1987 Metal–metal interactions among dietary toxic metals and essential trace metals. *Ecotoxicol Environ Safety* **14**, 275–287.

Felley-Bosco E, Diezi J. 1992 Dietary calcium restriction enhances cadmium-induced metallothionein synthesis in rats. *Toxicol Lett* **60**, 139–144.

Flanagan PR, McLellan JS, Haist J. *et al.* 1978 Increased dietary cadmium absorption in mice and human subjects with iron deficiency. *Gastroenterology* **74**, 841–846.

Foulkes EC. 1985 Interactions between metals in rat jejunum: implications on the nature of cadmium uptake. *Toxicology* **37**, 117–125.

Fox MRS, Tao SH, Stone CL, Fry BE. 1984 The effects of zinc, iron and copper deficiencies on cadmium levels in tissues of Japanese quail. *Environ Health Perspect* **54**, 57–65.

Groten JP, Sinkeldam EJ, Luten JB, van Bladeren PJ. 1991a Cadmium accumulation and metallothionein concentrations after 4-week dietary exposure to cadmium chloride or cadmium–metallothionein in rats. *Toxicol Appl Pharmacol* **111**, 504–513.

Groten JP, Sinkeldam EJ, Luten JB, Muys T, van Bladeren PJ. 1991b Interaction of dietary Ca, P, Mg, Mn, Cu, Fe, Zn and Se with the accumulation and oral toxicity of cadmium in rats. *Food Chem Toxicol* **29**, 249–258.

Hyvärinen H. 1972 Seasonal changes in the copper content of the liver of the common shrew, *Sorex araneus* over a two-year period. *J Zool (Lond)* **166**, 411–416.

Jacobs RM, Jones AOL, Fox MRS, Lener J. 1983 Effects of dietary zinc, manganese and copper on tissue accumulation of cadmium by Japanese quail. *Proc Soc Exp Biol Med* **172**, 34–38.

Kotsonis FN, Klaassen CD. 1978 The relationship of metallothionein to the toxicity of cadmium after prolonged oral administration to rats. *Toxicol Appl Pharmacol* **46**, 39–54.

Leon L, Johnson DR. 1985 Role of iron in jejunal uptake of cadmium in the newborn rat. *J Toxicol Environ Health* **15**, 687–696.

Meese GB. 1971 Some aspects of energy balance in the bank vole *Clethrionomys glareolus*. *J Zool (Lond)* **163**, 305–317.

Nordberg GF, Kjellström T, Nordberg M. 1985 Kinetics and metabolism. In: Friberg L, Elinder CG, Kjellström T, Nordberg GF, eds. *Cadmium and Health*, Vols 1 and 2. Boca Raton, FL: CRC Press; 103–179.

Panemangalore M. 1993 Interaction among zinc, copper and cadmium in rats: effects of low zinc and copper diets and oral cadmium exposure. *J Trace Elem Exp Med* **6**, 125–139.

Revis NW. 1981 The relationship of dietary protein to metallothionein and cadmium-induced renal damage. *Toxicology* **20**, 323–333.

Rimbach G, Brandt K, Most E, Pallauf J. 1995 Supplemental phytic acid and microbial phytase change zinc bioavailability and cadmium accumulation in growing rats. *J Trace Elem Med Biol* **9**, 117–122.

Rummler HG, Classen HG, Schimatschek HF, *et al.* 1989 Age-dependent accumulation of cadmium in rats exposed to contaminated drinking water; interactions with zinc and copper and subcellular Cd distribution in kidney cells. *J Trace Elem Electrolytes Health Dis* **3**, 217–223.

Sawicka-Kapusta K, Górecki A, Świergosz R, *et al.* 1987 Effect of metabolic rate on the rate of elimination of high and low concentrations of cadmium and lead in the bank vole. *Ekol Pol* **35**, 399–430.

Schenkel H. 1994 Toxicokinetics and toxicodynamic behavior of cadmium. *Proc Soc Nutr Physiol* **2**, 17–29.

Shaikh ZA, Jordan SA, Tewari PC. 1993 Cadmium disposition and metallothionein induction in mice: strain-, sex-, age- and dose-dependent differences. *Toxicology* **80**, 51–70.

Tahka KM. 1978 A histochemical study on the effects of photoperiod on gonadal and adrenal function in the male bank vole (*Clethrionomys glareolus*). *J Reprod Fertil* **54**, 57–66.

Washko PW, Cousins RJ. 1977 Role of dietary calcium and calcium binding protein in cadmium toxicity in rats. *J Nutr* **107**, 920–928.

Włostowski T. 1992 Seasonal changes in subcellular distribution of zinc, copper, cadmium and metallothionein in the liver of bank vole (*Clethrionomys glareolus*): a possible essential role of cadmium and metallothionein in the hepatic metabolism of copper. *Comp Biochem Physiol* **101C**, 155–162.

Włostowski T, Chętnicki W, Gierłachowska-Bałdyga W, Chycak B. 1988 Zinc, iron, copper, manganese, calcium and magnesium supply status of free-living bank voles. *Acta Theriol* **33**, 555–573.