Review article

Safe levels of cadmium intake to prevent renal toxicity in human subjects

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The present review attempts to provide an update of the scientific knowledge on the renal toxicity which occurs in human subjects as a result of chronic ingestion of low-level dietary Cd. It highlights important features of Cd toxicology and sources of uncertainty in the assessment of health risk due to dietary Cd. It also discusses potential mechanisms for increased susceptibility to Cd toxicity in individuals with diabetes. Exposure assessment on the basis of Cd levels in foodstuffs reveals that vegetables and cereals are the main sources of dietary Cd, although Cd is also found in meat, albeit to a lesser extent. Cd accumulates particularly in the kidney and liver, and hence offal contains relatively high amounts. Fish contains only small quantities of Cd, while crustaceans and molluscs may accumulate larger amounts from the aquatic environment. Data on Cd accumulation in human kidney and liver obtained from autopsy studies are presented, along with results of epidemiological studies showing the relationship between renal tubular dysfunction and kidney Cd burden. These findings suggest that a kidney Cd level of 50 μg/g wet weight is a maximum tolerable level in order to avoid abnormal kidney function. This renal Cd burden corresponds to a urinary Cd excretion of 2 μg/d. Accordingly, safe daily levels of Cd intake should be kept below 30 μg per person. Individual variations in Cd absorption and sensitivity to toxicity predicts that a dietary Cd intake of 30 μg/d may result in a slight renal dysfunction in about 1 % of the adult population. The previous guideline for a maximum recommended Cd intake of 1 μg/kg body weight per d is thus shown to be too high to ensure that renal dysfunction does not occur as a result of dietary Cd intake.

Dietary cadmium: Cadmium body burden: Kidney toxicity: Zinc homeostasis: Diabetic renal complications

FAO/WHO guideline on safe levels for intake of dietary cadmium

Cd is a non-essential heavy metal, occurring naturally in Zn and Pb ores and in some rock phosphate fertilizers (World Health Organization, 1989; Resource Sciences, 1997; McLaughlin & Singh, 1999). Industrial uses of the metal and agricultural activities have now led to its widespread dispersion at trace levels into the environment and human foodstuffs (Galal-Gorchev, 1993; Australia New Zealand Food Authority, 1998; Food and Agriculture Organization/World Health Organization, 1998). This environmental pollution by Cd has raised growing concerns about its effects on the health of the general population since its renal toxicity is well known (World Health Organization, 1989; International Programme on Chemical Safety, 1992; Staessen *et al.* 1996; Jarup *et al.* 1998). This concern has led to the establishment of a provisional tolerable weekly intake (PTWI). The Joint FAO/WHO Expert Committee on Food Additives defines the PTWI for a chemical with no intended function as an estimate of the amount of the chemical that can be ingested weekly over a lifetime

Abbreviations: MT, metallothionein; NAG, *N*-acetyl-β-D-glucosaminidase; PTWI, provisional tolerable weekly intake.

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without appreciable health risk (World Health Organization, 1989). This estimate is not a no-effect level; it provides an international guideline for monitoring global Cd pollution and assessing the potential health risk caused by Cd contamination of food. The PTWI first allocated to cadmium was 400–500 μg per person per week. This level was based on a critical concentration of 200 μg Cd/g kidney cortex, attainable after a dietary Cd intake of 140–260 μg/d for over 50 years or 2000 mg over a lifetime. In 1992, the PTWI was expressed more rationally in terms of the intake per kg body weight, corresponding to 7 μg/kg body weight per week or 1 μg/kg body weight per d (World Health Organization, 1992). In 1993, while the PTWI of 7 μg/kg body weight was retained (World Health Organization/Food and Agriculture Organization, 1993), it was recognised that the model on which the PTWI was based did not include a safety factor and that there was only a very modest safety margin between the exposure in a normal diet and the level of exposure that produces deleterious effects.

Assessment of dietary cadmium exposure

Levels of cadmium in foodstuffs

Cd appears as a contaminant in most foodstuffs (Galal-Gorchev, 1993; Resource Sciences, 1997; Australia New Zealand Food Authority, 1998; Food and Agriculture Organization/World Health Organization, 1998). The typical levels of the metal found in various kinds of food are shown in Table 1. Cd levels in most vegetables, including bulbs, roots and tubers, are usually below 0·05 mg/kg, although leafy vegetables such as spinach and lettuce may have considerably higher levels. Some wild mushrooms have been found to contain high levels of Cd (1 mg/kg), even when they grow in uncontaminated soil. The levels of Cd found in flour or bread are lower than the levels found in grain, because Cd is present mainly in the outer parts of the grain which is removed in the milling process. For the same reason, Cd levels are higher in wholemeal-type bread than other types. The average level of Cd in bread is below 0·1 mg/kg. Wheat, in particular durum wheat, may contain higher levels of Cd. Rice flour usually contains less than 0·1 mg/kg.

Oilseeds, such as sunflower seeds, peanuts (*Arachis hypagaea*) and linseed, accumulate Cd from the soil independent of the Cd concentration in the soil (Food and Agriculture Organization/World Health Organization, 1998). The Cd content in seed may exceed 0·5 mg/kg. Cd levels found in sunflower kernels range from 0·2–2·5 mg/kg (Li *et al.* 1995). Peanuts grown on soil low in Cd contain levels less than 0·05 mg/kg (Wolnik *et al.* 1983; Resource Sciences, 1997). In a similar manner to that of some oilseeds, tobacco (*Nicotiana* spp.) efficiently accumulates Cd in its leaves (Chaney *et al.* 1999). Cigarette smokers may therefore absorb large amounts of Cd via the lungs, in addition to dietary Cd via the gastrointestinal tract. Passive uptake of Cd from the respiratory system is estimated to be 50 % (Elinder *et al.* 1976; Ellis *et al.* 1985).

The Cd levels in meat from muscle are of the order of 0·01 mg/kg for animals at slaughter, although they may be higher in older animals. Cd concentrations in liver, and particularly, kidney are substantially higher than that in muscle. In the livers of calves, pigs and poultry, Cd levels range from 0·02 to 0·2 mg/kg; these levels may also be higher in older animals. Cd levels found in kidneys from calves and pigs range from 0·05 to 0·5 mg/kg, while the concentration in ox kidneys may approach 1 mg/kg. Horse kidney and liver may have Cd concentrations exceeding 10 mg/kg.

Cd concentrations reported for fish muscle are about 0·02 mg/kg, although higher levels are found in some species. Molluscs are known to accumulate Cd, independent of environmental pollution, and normally have a Cd concentration of 0·2 mg/kg. This concentration may be considerably higher, however, due to accumulation of Cd from contaminated waters (Food and Agriculture Organization/World Health Organization, 1998; Rayment, 1995). 'Brown' crab meat may contain Cd at levels above 10 mg/kg. For example, the hepato-pancreas of spanner crabs (*Ranina ranina*) was found to contain Cd at a level of 14·9 mg/kg (Rayment, 1995). Prawns captured in unpolluted or relatively-unpolluted Australian and international waters sometimes have Cd concentrations in excess of 0·2 mg/kg. The Cd content of bluff oysters (*Ostrea lutaria*) has been reported 27 mg/kg dry weight (McKenzie *et al.* 1986).

Based on the typical Cd content of the relevant foods, a

Table 1. Cadmium levels in foodstuffs and estimates of dietary cadmium exposure (adapted from Galal-Gorchev, 1993; Rayment, 1995; Food and Agriculture Organization/World Health Organization, 1998; Resources Sciences, 1997; Australia New Zealand Food Authority, 1998)

Food item	Cd level (mg/kg)		Intake level (g/d)	Extreme exposure (μg/d)	Typical exposure (μg/d)
	Maximum	Typical			
Vegetables, including potatoes	0·1	0·05	250	25	12·5
Cereals, pulses and legume, including rice and wheat grain	0·2	0·05	200	40	10
Fruit	0·05	0·01	150	7·5	1·5
Oilseeds and cocoa beans	1	0·5	1	1	0·5
Meat of cattle, poultry, pigs and sheep	0·1	0·02	150	15	3
Liver of cattle, poultry, pigs and sheep	0·5	0·1	5	2·5	0·5
Kidney of cattle, poultry, pigs and sheep	2	0·5	1	2	0·5
Fish	0·05	0·02	30	1·5	0·6
Crustaceans, molluscs	2	0·25	3	6	0·75
Total				93·5	30

Cd intake of 30 μg/d has been estimated for the 'average consumer' (Table 1). Cereals and vegetables, including potatoes, appear to account for more than 80 % of the estimated total Cd intake. Meat, especially offal, accounts for most of the remainder. Molluscs and crustaceans normally only constitute a small part of the diet, and are not considered to contribute much to the Cd intake. Fish contains small quantities of Cd, and is not a major source of dietary Cd. For the 'extreme' consumer Cd intake is estimated either by multiplying the typical exposure by 3 or by using the highest Cd levels found in all relevant foods. Such estimates give Cd intakes of 90 and 93·5 μg/d respectively. These dietary Cd levels illustrate the narrow safety margin between the level of exposure from a normal diet and the level likely to produce deleterious effects. There are particular concerns about the intake of Cd for vegetarians or those who habitually consume diets high in Cd, for example, due to high consumption of shellfish and some seafood.

However, based on data from the 1996 Australian Market Basket Survey (Australia New Zealand Food Authority, 1998), Cd intakes in the range of 9–15 μg/d were estimated for an average Australian consumer. Potatoes, wheat, cocoa and meat contributed 46, 16, 12 and 7 % of the Cd in the diet respectively, while crustaceans, liver, peanuts and vegetables each contributed 2–3 %, providing a further 11 % of the total intake. A similar dietary Cd intake of 10–14 μg/d was estimated for an average consumer in Germany, using data from the German Market Basket Survey (Muller *et al.* 1998). The relative contributions (%) of different food groups to dietary Cd intake in the German survey were as follows: bread, cake and pastries 41, potatoes 14, vegetables 10, meat, sausage and fish 9; similar to the Australian findings.

Database estimation of dietary Cd intake probably provides a reasonable method for estimating the relative contributions of different food groups to dietary Cd intake. Its use in health risk assessment, however, is questionable, because of individual variations in kidney Cd concentrations and sensitivity to Cd toxicity (Foulkes, 1993; Jarup *et al.* 1998; Chaney *et al.* 1999). Its use in exposure assessment needs to be validated by analysis of duplicate diets. In a study on a sample of the US population, the database calculation gave an estimate of a Cd intake of about 24 μg/d; while an actual analysis of duplicate diets estimated intake to be 56 μg/d (Reeves & Vanderpool, 1997). Thus, the database estimations in this instance underestimated dietary Cd intake levels by 50 % although the average Cd level of 56 μg in duplicate diets is within the current guideline for safe intake level of 1 μg/kg body weight per d.

Levels of cadmium in human kidneys and livers

An assessment of exposure to dietary Cd can also be validated by measurement of the levels of kidney Cd in the general population, since an average dietary intake appears to be strongly related to kidney Cd levels (Morgan & Sherlock, 1984). In two Australian autopsy studies an average Cd level of 40 μg/g wet weight was found in kidney cortex samples from a group of subjects aged upto 50 years (Miller *et al.* 1976; Spickett & Lazner, 1979). A toxico-kinetic-based model used to estimate the dietary intake of Cd suggested it was between 30 and 50 μg/d (Miller *et al.* 1976). Although the two Australian autopsy studies were carried out 20 years ago, and both smokers and non-smokers were included, there has been no indication of decreases in either food Cd content or dramatic changes in dietary habits in Australia in the last two decades. The Cd concentration in renal cortex samples from 40–50-year-old men ranged from 7 to 43 μg/g wet tissue weight in another autopsy study conducted recently. Of sixty-one subjects, two subjects, both women, had renal Cd concentrations of about 62 μg/g a concentration at which toxicity may occur (S Satarug, JR Baker, PEB Reilly, MR Moore and DJ Williams, unpublished results). Thus, the average dietary Cd intake of 9–15 μg/d derived from modelling of the 1996 Australian Market Basket Survey data (Australia New Zealand Food Authority,

Table 2. Human liver and kidney cadmium concentrations (μg/g wet tissue weight)
(Values are means, except in the study of Tiran *et al.* (1995) where values are medians)

	Age-group (years)						Reference	Country of origin
	Fetal (*n* 9)	1–20 (*n* 1)	21–40 (*n* 8)	41–60 (*n* 13)	>61–80 (*n* 52)	81–90 (*n* 6)	Chung *et al.* (1986)	Canada
Liver	ND	1·0	1·7	2·3	2·2	0·7		
Kidney	ND	5·4	26·3	41·8	16·4	6·8		
	12–18(*n* 2)	25–36(*n* 7)	45–59(*n* 7)	61–69(*n* 8)	70–79(*n* 8)	84–87(*n* 4)	Tiran *et al.* (1995)*	Austria
Liver	0·16	0·62	1·51	0·56	0·78	0·79		
Kidney	3·68	6·38	5·80	10·04	6·72	8·05		
	0–9(*n* 7)	10–29(*n* 56)	30–39(*n* 34)	40–59(*n* 83)	60–79(*n* 80)	80–99(*n* 31)	Elinder *et al.* (1976)	Sweden
Liver	0·26	0·56	0·60	0·77	1·04	0·59		
Kidney	2·39	8·83	17·96	19·92	15·02	7·06		
	0–1(*n* 6)	2–20(*n* 10)	21–40(*n* 10)	41–60(*n* 12)	61–95(*n* 12)		Yoshida *et al.* (1998)	Japan non-polluted area
Liver	0·05	1·12	2·29	1·88	3·55			
Kidney	0·61	8·41	33·3	69·8	52·3			

* Non-smokers only were included; all other studies included both smokers and non-smokers.

1998), appears to be too low to account for these recorded renal Cd levels in Australians.

Human liver and kidney Cd levels obtained from autopsy studies conducted in Canada, Austria, Sweden and Japan are summarized in Table 2. Occupationally-exposed subjects were not included in any of these studies. The Austrian study included only non-smokers, while the Canadian, Swedish and Japanese studies included both smokers and non-smokers. All three studies indicate that kidney Cd concentration increases progressively with age, reaching a peak at 40–60 years. Kidney Cd concentrations were lower in subjects over 60 years old than in those in some younger age-groups. Lower renal Cd levels in subjects over 60 years old may represent increased exposure to Cd in recent times. It may also represent Cd loss from damaged kidneys or age-related degeneration of kidneys, since no further accumulation of Cd was found in damaged kidneys despite continued exposure (Ellis *et al.* 1981). Under these conditions, the renal levels were found to fall, even though the amounts of Cd in the liver may continue to increase. In accordance with this view, Cd concentration in the kidneys of subjects dying of renal disease was found to be markedly lower than that from subjects dying of other diseases (Lyon *et al.* 1999).

The liver Cd concentration, although gradually increasing with age, does not show a decline in older age-groups. The average liver Cd concentration found in the 40–60 years age-groups ranges from 0·77 to 2·3 μg/g. In contrast to lower levels of liver Cd, the average kidney Cd content of the 40–60 years age-groups recorded in these studies range from 19·92 to 69·8 μg/g. These values were 20–40-fold greater than those for the liver. In the Austrian study, which included only non-smokers, the highest renal Cd concentration (10 μg/g kidney cortex) was found in the 61–69 years age-group. This value is 18-fold greater than the liver Cd level found in the same age-group. This consistent preferential accumulation in the kidney appears to be a feature of chronic exposure to low-level dietary Cd. It is attributable in part to slow mobilization of Cd from the liver and other tissues to the kidneys, probably in metallothionein (MT)-bound form (Dudley *et al.* 1985; Chan *et al.* 1993). Such preferential kidney accumulation has also been attributed to the role of intestinal MT (see p. 797).

In contrast to low-level dietary exposure, inhalation of Cd in dust and fumes in the workplace gives rise to high Cd levels in both the liver and kidney. Cd levels of 42·3 and 110 μg/g respectively were found in the liver and kidney of occupationally-exposed subjects (Ellis *et al.* 1984). These Cd levels give rise to a 50 % probability of having kidney damage and dysfunction (Ellis *et al.* 1984; Lauwerys *et al.* 1994). A more recent study in workers in the battery manufacturing industry confirms high Cd levels in both the liver and kidney as a feature of non-dietary exposure (Borjesson *et al.* 1997). In chronic low-level exposure a renal Cd level of 200 μg/g may give rise to a 10 % probability of having kidney dysfunction in some human populations (Ellis *et al.* 1983; Foulkes, 1993). In 'high-risk' groups, this renal Cd level, however, may give rise to a 50 % probability of having kidney dysfunction (Buchet *et al.* 1990; Jarup *et al.* 1998).

In the Swedish study (Elinder *et al.* 1976), it was noted that smokers had about 2-fold greater kidney Cd concentrations than non-smokers, and that most of the individuals with kidney Cd concentrations over 50 μg/g were women. A large British autopsy study (Lyon *et al.* 1999), which included only kidney samples, showed that levels in kidneys of smokers were on average 5 μg/g higher than those of non-smokers and the 40–59 years age-group had an average kidney Cd of 23 μg/g. Variations in renal Cd accumulation from cigarette smoke recorded in different human population studies may be due to varying Cd content of tobacco leaves (Elinder *et al.* 1983). The British study (Lyon *et al.* 1999) also suggested that kidney Cd levels were static over the 16-year period (1978–1993), but were higher than those found in studies done in the 19th and early 20th century. The distribution of kidney Cd concentrations was skewed, with about 3·9 % of the 2700 samples above 50 μg/g, although the population mean value for kidney Cd concentration was only 19 μg/g.

Data from human autopsy studies suggest that the biological half-life of kidney Cd is 30 years (Elinder *et al.* 1976). On this basis, a toxico-kinetic model of Cd uptake, distribution and excretion was developed, which includes an oral absorption rate of 5 % and a daily excretion rate of 0·005 % of the body burden, one-third of which is in the kidney (Elinder *et al.* 1978; Buchet *et al.* 1990). The model predicts that the Cd-level of 50 μg/g kidney cortex may be attained after 50 years on a dietary Cd intake of about 1 μg/kg body weight per d, which is equivalent to the current guideline for safe levels of dietary Cd intake (Elinder *et al.* 1976).

Renal toxicity and the maximum tolerable dose

Renal tubular damage caused by Cd is known to be irreversible (International Programme on Chemical Safety, 1992; Jarup *et al.* 1998). The damage causes decreased reabsorption capacity, and hence loss from the body of otherwise reabsorbed solutes. Such solutes may include MT with firmly bound Zn and Cu, and a range of low-molecular-weight compounds such as glucose, amino acids, phosphate, Ca, β_2-microglobulin, retinol-binding protein, and possibly vitamin C (International Programme on Chemical Safety, 1992; Lauwerys *et al.* 1994). Urinary excretion of the metal itself, along with other small solutes and enzymes of renal tubular origin, such as *N*-acetyl-β-D-glucosaminidase (NAG), therefore provide useful indicators of renal tubular function. The level of Cd excreted in the urine is considered to reflect body burden or long-term exposure, before development of renal damage, whereas blood Cd is an indicator of more recent exposure (Lauwerys *et al.* 1994; Jarup *et al.* 1998).

Manifestation of Cd toxicity, such as increased urinary excretion of low-molecular-weight proteins, e.g. β_2-microglobulin and retinol-binding protein, appear to be implicated in long-term prognosis. A 40–80 % increased annual mortality risk has been recorded for subjects with Cd-induced kidney damage in three different areas of Cd pollution in Japan (Iwata *et al.* 1992; Nakagawa *et al.* 1993, 1996; Nishijo *et al.* 1999). In addition, increased urinary Cd and β_2-microglobulin levels were found to be associated with mortality in a dose-dependent manner (Nishijo *et al.* 1999). Increased risk of renal stone formation has also been

found in subjects with occupational exposure to Cd (Staessen *et al.* 1996; Jarup *et al.* 1997, 1998). A parallel may be made with diabetic patients, who show increased urinary excretion of microalbumin, a symptom of abnormal capillary leakage. This factor is, in fact, an early warning of renal complications, subclinical or clinical morbidity, and mortality (Peters *et al.* 1996; Lupaz, 1997; Mogensen, 1998; Sheth, 1999). Early intervention can retard the progression of microalbuminuria to end-stage renal failure. Similarly, if Cd exposure is eliminated, or minimised, the progression to chronic renal failure may be prevented.

Analysis of the relationship between occurrence of renal dysfunction and urinary Cd excretion in the general population reveals that renal Cd levels associated with slight kidney dysfunction may be lower than previously estimated. The Cadmibel study (Buchet *et al.* 1990), conducted on 2327 subjects in Belgium during 1985–9, found a 10 % probability of having renal dysfunction when urinary Cd excretion exceeded 2–4 μg/d. This value was derived from a logistic regression of Cd renal burden (urinary Cd) and various indicators of renal damage, including urinary excretion of Ca, amino acids, NAG, retinol-binding protein and β2-microglobulin. More than 10 % of values were found to be abnormal when Cd excretion (μg/d) exceeded 1·92 for Ca, 4·29 for amino acids, 2·74 for NAG, 2·87 for retinal-binding protein and 305 for β2-microglobulin. In this study, a cut-off value of 283 μg/d for β2-microglobulin was used to reflect abnormal values (Buchet *et al.* 1990). The Japanese studies used a cut-off value of 1000 μg β2-microglobulin/g creatinine, the level at which renal impairment was considered to be irreversible. They found that urinary Cd levels exceeding 1·6–3·0 μg/g creatinine for men and 2·3–4·6 μg/g creatinine for women indicated an excess prevalence of renal dysfunction (Hayano *et al.* 1996; Yamanaka *et al.* 1998). A study in China found a 9·1 % increase in urinary excretion of β_2-microglobulin to be associated with a rise in urinary Cd excretion from 0–4 μg/g creatinine to 4–8 μg/g creatinine (Cai *et al.* 1998).

The levels of urinary Cd found to be associated with excess risk of renal tubular dysfunction in these studies correspond to a kidney Cd level of ≥50 μg/g kidney cortex (Buchet *et al.* 1990). This value is well supported by one recent autopsy study conducted on thirty-nine subjects, 10–72 years of age, which found a urinary Cd level of 1·7 μg/g creatinine in subjects with a kidney Cd level of 50 μg/g (Orlowski *et al.* 1998). The use of urinary Cd to give some estimates of renal Cd burden also proved to be valid in a study of 30–59-year-old non-smoking Korean women (Moon *et al.* 1998, 1999). Thus, it is reasonable to infer from these studies that renal Cd of approximately 50 μg/g is a maximum tolerable internal dose to avoid abnormal kidney function. This level corresponds to a urinary Cd excretion of 2 μg/d. Strong correlations between concentrations of Cd in rice and significant increases in urinary excretion of β_2-microglobulin, glucose, amino acids and MT were found in Japanese people who had lived in Cd-polluted areas for at least 30 years and consumed home-grown rice (Nakashima *et al.* 1997). Further, regression analysis of data revealed that the Cd content of rice needed to be less than 0·4 mg/kg in order to avoid occurrence of renal dysfunction (Nakashima *et al.* 1997). Evidence for Cd renal toxicity was found in a sample of the Chinese population who consumed rice containing Cd at a level of 3·7 mg/kg (Nordberg *et al.* 1997). This level is approximately 10-fold greater than the safe limit suggested in the Japanese study (Nakashima *et al.* 1997).

Nephrotoxic potential of cadmium in sunflower kernels *v.* bluff oysters

Cd accumulation and toxicity in the kidney is known to be a function of the chemical form of the metal and the presence of certain other elements in the diet, as well as individual sensitivity (Buchet *et al.* 1990; Foulkes, 1993; Jarup *et al.* 1998; Chaney *et al.* 1999). Apart from Cd in rice, our knowledge of the nephrotoxic potential of Cd in other foodstuffs is very limited. The studies on Cd in sunflower kernels and bluff oysters discussed in the present review are among the few studies that have been done in human subjects. Due to inherent genetic and physiological characteristics, sunflower has a high rate of Cd uptake from soil, and this is deposited in the kernels (Li *et al.* 1995). Thus, sunflower kernel has a higher concentration of Cd than most other grains, ranging from 0·2 to 2·5 mg/kg wet weight.

The bioavailability of Cd in sunflower kernels has been demonstrated in rats (Reeves *et al.* 1994) and a study of the nephrotoxic potential of sunflower kernels was performed in subjects who habitually consume sunflower kernels (Reeves & Vanderpool, 1997). Seventy-five male and female non-smokers, aged 30–70 years, were included in the study. Based on a self-reported food-frequency survey, subjects who reported consuming more than 28 g sunflower kernels per week were classed as high consumers. Actual analysis of duplicate diet showed that control subjects who consumed few sunflower kernels had an average dietary Cd intake of 36 μg/d. However, food analysis was not done for any of the high consumers. Blood concentrations and urinary excretion of Cd were used as indicators of Cd body burden. The urinary excretions of β_2-microglobulin and NAG were used as markers for Cd toxicity and evidence of renal toxicity was found in the high consumers. The limited number of subjects recruited in the study and individual variations in Cd absorption, however, meant that the expected increased Cd body burden among the high consumers could not be demonstrated.

Cd toxicity may occur if the Cd in sunflower kernels is absorbed and delivered to kidneys in an MT-bound form (Cd_7MT), since the rate at which Cd is presented to the kidneys has been shown to be important in the manifestation of toxicity of this metal (Wahba & Waalkes, 1990; Foulkes, 1993; Sudo *et al.* 1994). In chronically-exposed rats hepatic damage was found to precede nephrotoxicity, and hence hepatic Cd probably reached the kidneys largely in the hepatic MT-bound form (Dudley *et al.* 1985). In the protein-bound form, up to seven Cd atoms/mol MT gain entry to the proximal tubule cells. To support this hypothesis, injection of Cd-bound MT has been shown to result in greater accumulation of renal Cd and renal damage than equimolar injections of $CdCl_2$ (Dorian *et al.* 1992; Wang *et al.* 1993). Further, acute renal toxicity can be

induced in rats by a single injection of Cd (0·3–0·4 mg/kg body weight) bound to MT either with Zn (Cd_5Zn_2MT) or without Zn (Cd_7MT). These treatments gave rise to renal Cd concentrations of only 5–9 μg/g (Sudo *et al.* 1994; Liu *et al.* 1998). Taken together, the results of these studies indicate that Cd in sunflower kernels may have a high nephrotoxic potential. Alternatively, they may indicate increased sensitivity to Cd toxicity in the high sunflower-kernel consumers.

Another study, conducted on subjects associated with the oyster industry in New Zealand (McKenzie *et al.* 1986), investigated the short-term (6 months) relationships between intake of high-Cd foods (bluff oysters), Cd body burden, and toxicity. The study included fifty-seven men and nineteen women in the age range 20–75 years. Based on their oyster intakes, the subjects were divided into four groups with average consumptions of <6, 6–24, 24–<72 and ≥ 72 oysters per week for groups 1, 2, 3 and 4 respectively. The estimated Cd intake (μg/d) for subjects in groups 1, 2, 3 and 4 were 34, 75, 116 and 250 respectively. The concentration of Cd in whole blood was found to be higher in smokers than in non-smokers. In the non-smokers, the increase in whole-blood Cd attributable to oyster consumption was 1·2 μg/l for subjects in group 4. The concentration of Se in whole blood was also elevated by oyster consumption, but serum concentrations of Zn or Cu were not affected. The concentrations of Cd, Zn and β_2-microglobulin in the urine were not affected, and there was no glycosuria or proteinuria that was attributed to a high Cd intake. None of the subjects had a β_2-microglobulin concentration greater than 250 μg/l. Hair Cd, Zn and Cu levels were not affected by oyster consumption. It was concluded that interactions with Se and other trace elements in oysters may result in diminished absorption of Cd. Although dietary Se and Zn were measured in the study, other important determinants of Cd absorption and renal accumulation, such as Fe content in the oysters and Fe status of the subjects, were not taken into account. Furthermore, short-term effects and the small number of subjects, especially women, did not allow demonstration of the expected increased Cd body burden among the high bluff oyster consumers. Nevertheless, it showed that the bioavailability of Cd in bluff oysters appeared to be relatively low. However, truly comparative bioavailability of Cd in different foods cannot be made based on human study data because of known individual variations in absorption.

Absorption as a potential source of variation in renal cadmium burden

The absorption rate of Cd is estimated to be between 3 and 7 % in human subjects and 0·3–3·5 % in rat (World Health Organization, 1989; International Programme on Chemical Safety, 1992). A 5 % absorption rate has been used in health-risk assessment procedures and this level is considered to be conservative. Recent studies, however, indicate that up to 20 % of the Cd may be absorbed from the gastrointestinal tract (Diamond *et al.* 1997). Also, the British autopsy study (Lyon *et al.* 1999) showed that individual variations in dietary intake, absorption, and excretion of Cd account for a large percentage (about 92 %) of the variation in renal Cd accumulation, while age and smoking were found to explain only 8 % of the variation. The rate of mobilisation of liver Cd to the kidney may be variable among individuals, and this variability may need to be considered as another potential source of variation in renal Cd burden. A study in our own laboratory (S Satarug, JR Baker, PEB Reilly, MR Moore and DJ Williams, unpublished results) using a variant strain of Wistar rats that has lost the ability to synthesise vitamin C, suggested that vitamin C status and NO production in response to immunostimulants may enhance mobilisation of Cd to the kidney.

Role of individual status for micronutrients and essential elements in absorption

Age, status of micronutrients and essential elements, notably vitamin C, Fe, Ca, and Zn, have been found to influence Cd absorption (Elsenhans *et al.* 1997; Brzoska & Moniuszko-Jakoniuk, 1998). The rate of Cd absorption is increased substantially when the body is in short supply of elements with common absorption and transport mechanisms. This increased absorption has been demonstrated in subjects with dietary Fe deficiency (Flanagan *et al.* 1978; Vahter *et al.* 1996). Increased absorption of Cd from a high-shellfish diet was found in women with low body Fe stores (Vahter *et al.* 1996). Cd intake levels, assessed by duplicate diets, were found to be 11 and 28 μg/d respectively for women in the mixed-diet and high-shellfish diet groups respectively. No differences in blood or urine concentrations were seen in the two groups when all subjects were considered. However, a 63 % increase in blood Cd concentration and a 24 % increase in urine Cd concentration were found in women who consumed high-shellfish diets and had a plasma ferritin level of less than 20 μg/l compared with those who consumed mixed diets and had the same low body Fe stores (Vahter *et al.* 1996). Several studies have shown that women have higher concentrations of Cd in blood, urine and kidneys than men (Elinder *et al.* 1976; Watanabe *et al.* 1989; Buchet *et al.* 1990; Lin *et al.* 1995; Jarup *et al.* 1998). In general, women have lower body Fe stores than men, and hence the increased body Cd burden in women may be due to increased absorption and/or other toxico-kinetic variables (Jarup *et al.* 1998; Jin *et al.* 1998). One recent study reported that female Balb/c mice infected with Coxsackie virus showed a 70 % increase in absorption of Cd when Cd was administered by intubation at the dose of 0·3 μg/kg body weight, using ^{109}Cd as a tracer (Glynn *et al.* 1998). In the same study Cd absorption was found to be tripled at a Cd dose of 750 μg/kg body weight.

Individuals with haemochromatosis who absorb abnormally high amounts of Fe from foods may also absorb more Cd. Recently, the intestinal protein involved in dietary Fe absorption (Nramp2) has been reported to bind to many divalent ions, including Cd and Pb (Gunshin *et al.* 1997; Fleet, 1998; Wood & Han, 1998). Increased expression of Nramp2 in subjects with haemochromatosis or low body Fe stores in general, would provide them with a greater capacity to absorb Fe and possibly Cd.

Similarly, increased expression of Ca-binding protein in the epithelium of intestinal villi could enhance Cd absorption, whereas high dietary Ca could compete with the binding of Cd by the protein, and hence lower Cd absorption (Brzoska & Moniuszko-Jakoniuk, 1998). The interactions between dietary Cd and components in Ca absorption remain to be elucidated, especially in human subjects.

Role of intestinal metallothionein

It has been proposed that intestinal MT may play an important role in absorption, transport and distribution of dietary Cd to the kidney (Elsenhans *et al.* 1992, 1997). If this mechanism is in operation, dietary Cd would be deposited directly in the kidneys since Cd in MT-bound forms (Cd_7MT and Cd_5Zn_2MT) has been shown to be taken up largely by kidney (Dorian *et al.* 1992; Sudo *et al.* 1994; Liu *et al.* 1998). This hypothesis appears to challenge the previous notion that hepatic Cd accumulation takes place before renal accumulation. However, only high oral doses of Cd salts appear to give initially high liver Cd levels. In contrast, higher levels of Cd were seen in kidney than liver in rats fed the diet containing Cd at levels of 0·03–3 mg/kg (Scheuhammer, 1988; Elsenhans *et al.* 1992, 1997). These levels of Cd in rat diets are similar to those found in human foodstuffs (see Table 1). Also in rats, Cd levels were found to be higher in the kidney than in the liver 1, 4 and 8 months after feeding with contaminated rice containing Cd in the range 0·1–1·0 mg/kg (Hiratsuka *et al.* 1999). Higher Cd levels were found in the kidney than in the liver in every age-group in the human autopsy studies conducted on non-occupationally-exposed subjects (Table 2).

If intestinal MT plays an important role in dietary Cd absorption and renal accumulation, variability in the amount of Cd absorbed from various foods may be accounted for by the capacity for different food components to affect expression of this intestinal protein. Although there is little information on levels of intestinal MT in human subjects, the very high degree of inducibility of this protein in the liver is well-known (Bremner, 1993; Kagi, 1993; Cousins, 1994; Palmiter, 1998). Correlations between liver MT, Cd and Zn levels found in human autopsy studies suggest that Cd may have induced increases in MT levels in the liver (Chung *et al.* 1986; Lopez-Artiguez *et al.* 1995; Torra *et al.* 1995; Yoshida *et al.* 1998). Increased expression of MT was found in erythrocytes and monocytes from 19–35-year-old men who had received Zn supplements at a dose of 50 mg/d for 18 d (Sullivan *et al.* 1998). In rats, intestinal MT has been found to be induced by Cd, Zn and Cu, but not by Ni or Pb (Tandon *et al.* 1993).

Dietary flavonoids have been shown to interact with Cu and Fe, as well as to influence expression of MT (Kuo *et al.* 1998). Quercetin decreased MT levels in cultured human intestinal cells Caco-2, while genistein and biochanin increased the protein levels. The role of flavonoids in Cd absorption, however, remains to be elucidated. In contrast, Ca, Zn, Fe and fibre levels in the diet have been found to have a strong influence on Cd absorption and renal accumulation (Wing, 1993; Rimbach & Pallauf, 1997; Brzoska & Moniuszko-Jakoniuk, 1998; Lind *et al.* 1998). The mechanism for these interactions remains unclear.

A 70–80 % reduction in Cd accumulation in the liver and kidneys was found in rats after 8 weeks of feeding Cd-containing food supplemented with Ca, P, Fe and Zn (Groten *et al.* 1991). The reduction in Cd accumulation was attributed to the presence of Fe^{2+}. The addition of vitamin C improved Fe uptake, but did not decrease Cd accumulation. Fe in combination with Ca, P and Zn gave the most pronounced effect. In this study, however, high doses of Cd were used (the daily intake of Cd was 0·17–0·36 mg per rat, equivalent to 1·5–2·5 mg Cd/kg body weight per d). It remains to be seen whether such an effect of Fe on Cd accumulation is present at Cd levels close to the current Food and Agriculture Organization/World Health Organization (1998) recommended safe level of intake (1 μg/kg body weight per d). Nevertheless, this study calls for special consideration to be given to an adequate intake of Fe in the health-risk assessment of Cd in foods.

Diets high in phytate (high in fibre) have been found to enhance absorption and retention of Cd in the kidney in some experimental animals (Rimbach & Pallauf, 1997). Such effects require further studies involving a wider range of fibre sources and animal species, since they could be of particular concern to the general human population, in which dietary habits are changing towards higher intake of fibre-rich foods. Supplementation of food commodities with citric acid, which is a common practice, enhances the bioavailability of essential metals such as Zn, and may also result in increased absorption of Cd (Walter *et al.* 1998).

Interaction between renal cadmium burden and diabetes mellitus

The Cadmibel study in Belgium revealed for the first time that diabetic patients show increased susceptibility to the renal toxicity of Cd (Buchet *et al.* 1990). Subsequent animal studies have shown that the symptoms of diabetic renal complications and Cd renal toxicity are enhanced when both the metal and the disease are present. Injection of Cd bound to MT resulted in increased urinary excretion of proteins and Ca in both diabetic obese mice and non-obese littermate controls (Jin *et al.* 1994). In the diabetic obese mice, however, about 4-fold lower Cd doses gave the same increases in urinary excretion of proteins and Ca as those of the controls. In both groups, the Cd treatment resulted in increases in urinary glucose excretion in a Cd-dose-dependent manner, despite decreases in blood glucose and insulin. Thus, such findings suggest that glycosuria may be an indicator of the nephrotoxicity of Cd, particularly in experimental diabetes. Hereditary diabetic Chinese hamsters also appeared to be more susceptible to Cd renal toxicity (Jin & Frankel, 1996). In type I Diabetic rats, kidney Cd concentrations of 10–40 μg Cd/g wet weight were found to enhance urinary excretion of albumin, transferring and immunoglobulin, a feature of diabetic renal complications (Bernard *et al.* 1991). However, no Cd-related toxicity was seen at any of these renal Cd concentrations. Hence, a Cd renal burden at levels lower

than the threshold for toxicity (less than 50 μg/g wet weight in human subjects) may enhance development of diabetic renal complications without concurrent nephrotoxicity. The mechanisms underlying the involvement of Cd in the development and progression of diabetic nephropathy need further study.

Increased tissue Zn concentrations following Cd induction of the metal-binding protein MT may lead to changes in the activity of Zn-dependent enzymes in glucose metabolism, most probably in the liver. A deficit in hepatic gluconeogenesis has been observed in MT-null mice that cannot accumulate Zn in the liver and lose hepatic Zn in response to endotoxin injection (Philcox *et al.* 1995; Rofe *et al.* 1996). This observation supports the role of Zn and a 11·5 kDa Zn-binding protein in hepatic glucose metabolism (Brand & Heinickel, 1991). Incubation of hepatocytes from rats fed Zn increased the rate of lactate and glucose production (Brand & Kleineke, 1996). Cd concentrations ten times lower than those of Zn (8 μM *v.* 80 μM) gave the same effect, probably via a Zn-displacement mechanism due to their similar chemistry, but Cd has a higher affinity for S ligands than Zn (Waalkes *et al.* 1992). Indeed, Cd has been shown to displace Zn in the Cys_2Cys_2- and Cys_2-His_2-Zn fingers of steroid hormone and transcription factor III A (Hanas & Gunn, 1996). Our own study conducted on male Wistar rats showed that Cd displacement of Zn bound to renal MT occurs under *in vivo* conditions (Satarug *et al.* 2000). The effects of Cd on enhanced gluconeogenesis have yet to be shown in the kidney. Such studies may explain the glycosuria caused by injection of Cd-bound MT in obese diabetic and non-obese littermate control mice discussed earlier (p. 797).

In the Cadmibel study, individuals with a high body Cd burden, as assessed by urinary Cd, had on average 5 % lower serum Zn levels (Thijs *et al.* 1993; Staessen *et al.* 1996). This result was obtained after adjustment for effects of age and other significant covariants, and was not altered when occupationally-exposed subjects were excluded from the analysis. Redistribution of Zn from the labile pool into tissue, particularly the liver, probably caused the small reduction in serum Zn. In support of tissue redistribution, Zn, Cd and MT levels in human livers were found to be positively correlated (Chung *et al.* 1986; Lopez-Artiguez *et al.* 1995; Torra *et al.* 1995; Yoshida *et al.* 1998). In diabetic patients similar perturbations of Zn homeostasis may occur (Wolff, 1993; Isbir *et al.* 1994; Williams *et al.* 1995; Escobar *et al.* 1995). High-dose Zn supplementation, however, was found to be potentially toxic in insulin-dependent diabetic patients. The levels of haemoglobin A_{1c} in these patients were increased markedly after 28 d of Zn supplementation at 50 mg/d (Cunningham *et al.* 1994). Hence, protein glycosylation appeared to be enhanced when Zn was in excess. Higher levels of glycosylated haemoglobin such as haemoglobin A_{1c} have been associated with an increased risk of microvascular and macrovascular complications (Peters *et al.* 1996).

Renal Cd toxicity was found to be more pronounced in vitamin-C-deficient guinea-pigs than in those fed diets sufficient in the vitamin (Nagyova *et al.* 1994). This finding suggests a role for vitamin C in the prevention of Cd toxicity, although the biochemical mechanism for such a protective role of vitamin C remains unclear. Diabetes is known to be associated with a marginally reduced vitamin C status (Will *et al.* 1999), which may be one of the factors explaining the increased susceptibility to renal Cd toxicity (Buchet *et al.* 1990). Indeed, diabetic patients with clinical nephropathy were found to have lower mean plasma vitamin C levels, due to higher renal clearance of vitamin C, than those with microalbuminuria (Hirsch *et al.* 1998). However, Cd toxicity in the renal tubular system also promotes renal vitamin C clearance. Hence, plasma vitamin C levels might be further reduced in diabetic subjects with a high Cd body burden. A shortened onset time to renal failure may result.

High incidence of renal disease and dietary cadmium: are they linked?

Renal disease and diabetes, particularly the non-insulin-dependent type, are major health problems faced by Australian Aboriginals (Spencer *et al.* 1998). Diabetes affects 8–24 % of indigenous Australians, compared with 3–4 % among non-indigenous Australians. Torres Strait Islanders, who live in the northern tip of Queensland, suffer from even higher rates of diabetes. A much higher mortality rate has also been recorded among diabetic Aboriginals as compared with non-diabetic Aboriginals and non-Aboriginals with or without diabetes. The major cause of mortality has been renal disease. The complex causes of this disease are not fully understood, but it has been suggested that diabetic nephropathy, as well as infection, high insulin exposure, poor nutrition, smoking and high blood pressure, may be involved. In general, the median age for onset of renal failure is lower in indigenous Australians than their non-indigenous counterparts, and the condition has a higher incidence among women. Tiwi residents of Bathurst and Melville islands, north of Darwin in Northern Territory, have escalating rates of end-stage renal disease (Spencer *et al.* 1998).

As previously mentioned, crustaceans and molluscs are filter feeders and absorb large quantities of Cd from contaminated waters and sediments. Larger sea animals, including dugongs (*Dugong dugon*) and turtles, also accumulate large amounts of Cd (Dight & Gladstone, 1993; Gordon *et al.* 1998). The very high levels of Cd in seafood, especially in offal of dugongs and turtles, (7–76 mg/kg wet weight) have raised particular concerns, because they constitute a highly-valued component of the traditional diet of Torres Strait Islanders and some coastal Aboriginals. High levels of Fe (12–71 mg/kg dry weight) have also been found in offal of dugongs (Webb *et al.* 1999), and this factor may have a considerably effect on Cd absorption. To date, the role the high Cd levels in traditional foods plays in the development of renal disease in Australian Aboriginals has not been well studied. However, diabetic individuals are at a high risk of Cd-induced renal tubular dysfunction. Further, if dietary Cd does have a role, women are more likely to be affected than men, due to increased Cd absorption associated with lowered body Fe stores.

Concluding remarks

Individual variations in sensitivity to toxicity and kidney Cd accumulation found in human population studies suggest that a considerable number of individuals may have toxic levels of Cd in their kidneys, despite the modest population mean values for Cd body burden. If Cd pollution continues to increase, so will human dietary Cd exposure, and renal tubular dysfunction is likely to become more prevalent in human populations in the next 10–20 years, particularly in high-risk groups such as those with diabetics and those with poor vitamin C status, low body Fe stores, haemochromatosis and marginal Ca or Zn intake. There is a lack of therapeutically-effective chelating agents to enhance excretion of Cd from the kidneys, and this factor makes prevention of kidney Cd accumulation pivotal. The persistence of this metal in the environment requires a long-term approach to minimise human exposure through environmental management and maintenance of lower Cd levels wherever possible.

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