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## Chronic renal failure in Sri Lanka caused by elevated dietary cadmium: Trojan horse of the green revolution

J.M.R.S. Bandara<sup>a,b,\*</sup>, H.V.P. Wijewardena<sup>b</sup>, J. Liyanage<sup>c</sup>, M.A. Upul<sup>c</sup>, J.M.U.A. Bandara<sup>d</sup>

<sup>a</sup> Department of Agric. Biology, University of Peradeniya, Peradeniya, Sri Lanka

<sup>b</sup> Board of Study in Plant Protection, University of Peradeniya, Peradeniya, Sri Lanka

<sup>c</sup> Department of Chemistry, University of Kelaniya, Kelaniya, Sri Lanka

<sup>d</sup> Pediatrics Ward, Teaching Hospital, Peradeniya, Sri Lanka

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### ABSTRACT

The endemic of chronic renal failure (CRF) emerged in 2002 in the farming provinces of Sri Lanka. An estimate of dietary cadmium intake was between 15 and 28  $\mu\text{g}/\text{kg}$  body weight per week. The mean urinary cadmium in patients diagnosed with stage 5 kidney failure was 7.6  $\mu\text{g}/\text{g}$  creatinine and 11.6  $\mu\text{g}/\text{g}$  for asymptomatic persons. The agrochemical triple superphosphate (TSP) fertilizer containing 23.5–71.7 mg Cd/kg was the source of cadmium added to soils. Mean Cd content in cultivated vs. uncultivated soils in Anuradhapura district was  $0.02 \pm 0.01$  vs.  $0.11 \pm 0.19$  mg/kg while in Polonnaruwa district, it was  $0.005 \pm 0.004$  vs.  $0.016 \pm 0.005$  mg/kg. Prior to the Green Revolution, the amount of fertilizer used in rice cultivation in 1970 was 32,000 metric tons (Mts) rising to 74,000 Mts in 1975. Up to 68.9 Mts of Cd could have entered into the rice-cascade reservoir environment from TSP use since 1973. Diversion of the Mahaweli River in 1970–1980 further increased cadmium input. Cadmium transfer from Upper Mahaweli water to Polgolla was 72.13 kg/day. Cadmium content of the sediments from reservoirs collecting cadmium from irrigated TSP fertilized crop fields (rice and vegetables) was 1.8–2.4 mg/kg.

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### 1. Introduction

Chronic renal failure (CRF) is considered to be a worldwide public health problem. At present, the prevalence of end-stage renal failure is reaching epidemic levels in the North Central Province (NCP) of Sri Lanka. The only process of sustaining life when at the end stage or the popularly known as fifth stage CRF, is routine dialysis or kidney transplantation. Type II diabetes and hypertension still remain the main causes of CRF. Due to the asymptomatic nature, CRF is not easily detected until it is at the end stage, resulting in lost opportunities for prevention. Treatments of infections like hemorrhagic fever with renal syndrome and Hantaviruses prevalent under tropical environments are complicated by renal diseases. Overuse and misuse of agrochemicals contribute to both acute and chronic renal failure. The ingestion of various fungi and fruit has been associated with renal injury (Eiam-Ong and Sitprija, 1998). In Thailand, renal tubular acidosis and renal stone disease have been reported (Vasuvattakul et al., 1996). Renal tubular acidosis also has been reported in areas of Papua New Guinea (Brown

and Polume, 1994). In NCP of Sri Lanka chronic tubulointerstitial nephritis is common. Becker (2009) further reports that it is similar to aristolochic acid nephropathy, but without evidence of fungal ingestion. As reported by Wanigasuriya et al. (2009), in Sri Lanka, chronic renal failure not associated with diabetes, hypertension or snake bite was first reported in 2001, among the farmers in the major farming area under irrigation in NCP. It was first categorized as a chronic kidney disease of unknown etiology, following the format of Balkan Nephropathy which had similar ambiguous etiology (Athuraliya et al., 2009). However, the Balkan Nephropathy problems restricted to Bulgaria, Rumania and former Yugoslavia were later identified as a rare condition due to a Corona virus EBNV (Uzelac-Keserovi et al., 1999).

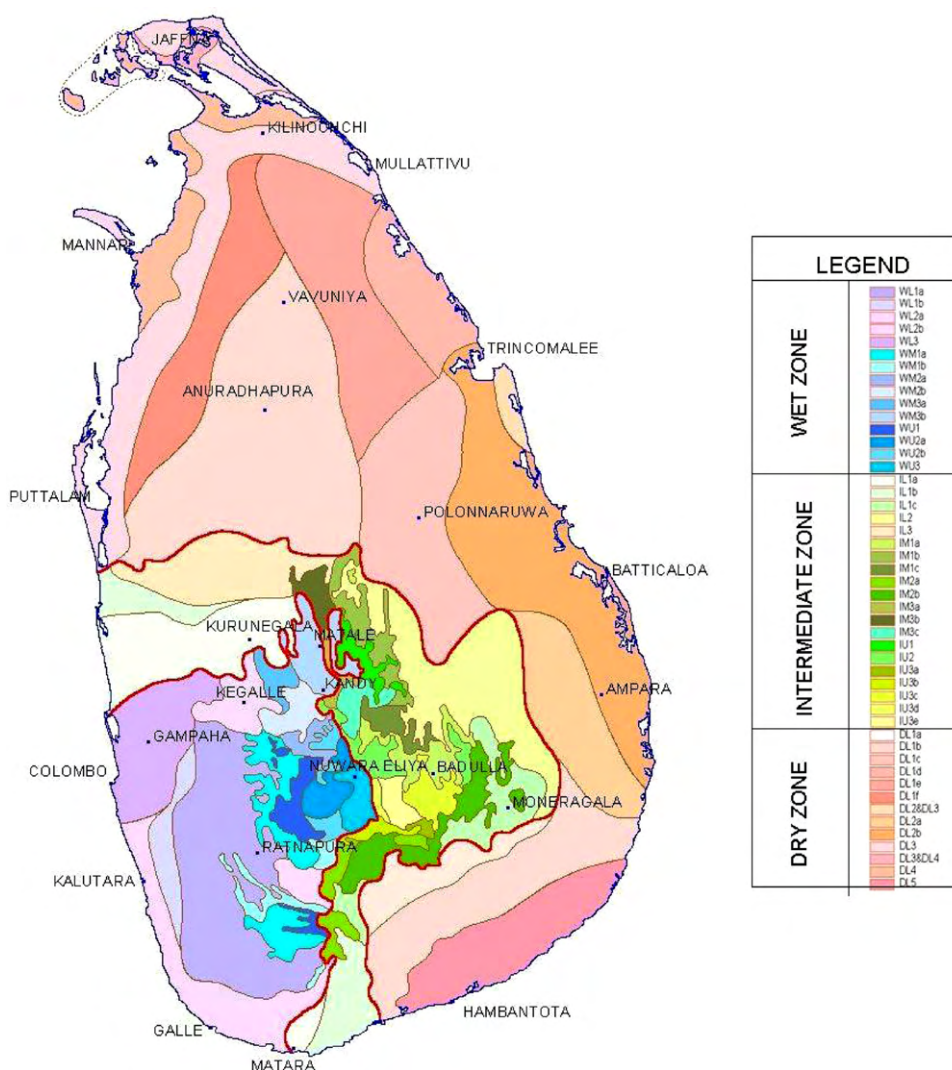
Research done during the past 40 years has established the relationship of dietary cadmium especially Cd contaminated rice and chronic renal failure (Shimada et al., 1977; Tohyama et al., 1982; Hochi et al., 1995; Osawa et al., 2001; Satarug and Moore, 2004; Simmons et al., 2005).

### 2. Cadmium in the environment

Persistence of elevated levels of cadmium in the environment is usually associated with geological occurrences or due to point pollution by industrial waste mostly due to Zn mining (Baker et al., 1977). However, there are no reports of high natural cadmium

\* Corresponding author at: Department of Agric. Biology, University of Peradeniya, Old Galaha Road, Peradeniya 20400, Sri Lanka. Tel.: +94 812395241; fax: +94 812388041.

E-mail address: [bandara.sarath@gmail.com](mailto:bandara.sarath@gmail.com) (J.M.R.S. Bandara).



**Fig. 1.** Agro ecological zones of Sri Lanka. The central highlands in the wet zone form the main catchment of Mahaweli River that was diverted to supplement the irrigation requirement of the farm lands in the Anuradhapura and Polonnaruwa districts (North Central Province) in the dry zone.

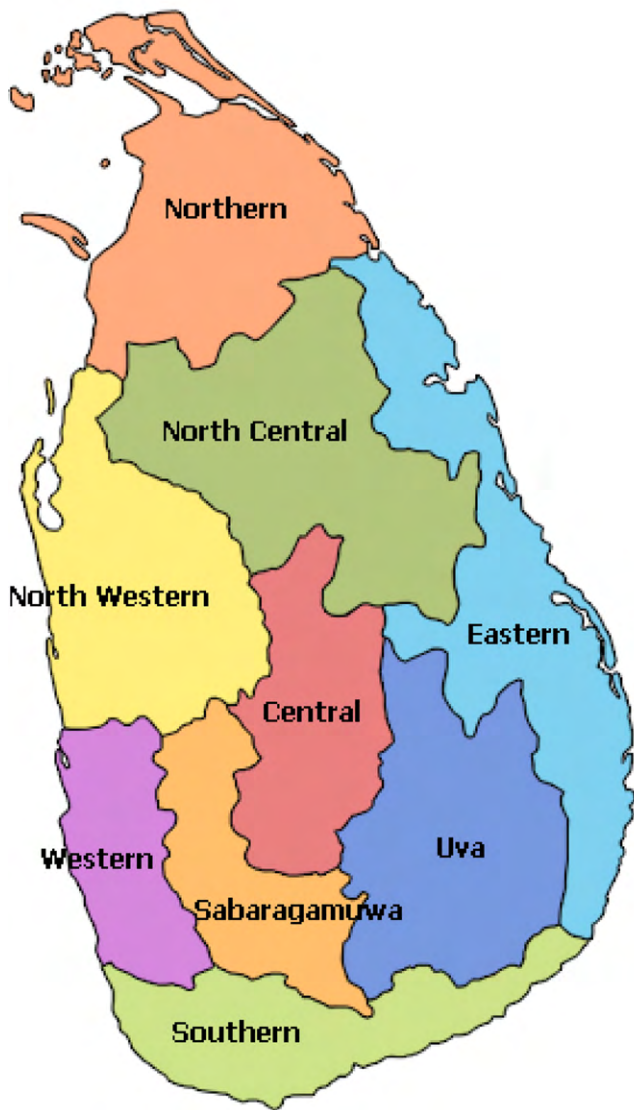
contamination in Sri Lankan soils nor are there any zinc mining industries on the island. Therefore the occurrence of chronic renal failure associated with elevated dietary cadmium required detailed investigation on the levels and sources of cadmium in the environment.

### 2.1. Cadmium in rivers and its impact on reservoirs

In the NCP 4000 water reservoirs, arranged in 280 separate cascades provide both irrigation and drinking water. Most are fed with the water from the Mahaweli River that originates in the central highlands of Sri Lanka (Fig. 1). Diverted Mahaweli River with a total catchment area of 10,000 km<sup>2</sup> is passing through five provinces to reach NCP reservoirs after the 1970–1977 river diversion scheme adopted by Sri Lanka. An analysis of water samples collected from 21 tributaries of this river, showed that all the catchment areas contributed to its Cd load. The degree of contamination ranged from 5.1 to 23 µg/l. The minimum Cd contamination occurred in predominantly tea growing areas of the watershed, probably due to low input of Cd from the type of phosphate fertilizer used in tea plantations. Tea estates used direct unprocessed rock phosphate, namely Eppawala Rock Phosphate (ERP) at the rate of 123 kg/ha. The ERP is a rock phosphate obtained from a phosphate ore in Eppawala, Anuradhapura, Sri Lanka and it contains only 1.7 mg of

Cd/kg compared to imported triple superphosphate a rock phosphate treated with sulphuric acid. TSP contains 23.5–71.7 mg/kg of Cd (Bandara et al., 2008; Premarathne, 2006). The total cadmium loading to the Mahaweli River from the catchment area in 1 year was estimated and was found to depend on the fertilizer regimes used in each cropping system, type of phosphate fertilizer, and the level of Cd present in the agrochemicals used. Mean Cd content of TSP used is 47 mg/kg based on the range 23.5–71.7 mg Cd/kg of TSP. Cadmium loading by the catchment under different farming systems as g/ha/year for rice = 26,479, tea = 23,987, vegetables and home gardens = 628,701 (Bandara et al., submitted for publication). The exchangeable Cd level in the upcountry soil varied from 0.32 to 1.24 mg/kg and the mean cation exchange capacity ranged from 11.7 in uncultivated soil to 36.4 cmol(+) per kg—centimole of positive ions per kg of soil (formerly milliequivalent of ions per 100 g), in soils cultivated with vegetables (Premarathne, 2006).

The Cd level at the Polgolla diversion canal to NCP was found to be 10.8 µg/l. At an average flow 6.679 million cubic meters per day, the potential transfer of cadmium from Upper Mahaweli water to NCP from Polgolla alone is 72.13 kg/day. The total cadmium was taken to reservoirs in NCP from both the cadmium input from TSP fertilized crop fields (rice and vegetables) in the NCP and the diverted River Mahaweli eventually settled in the sediments of reservoirs (1.77–2.45 mg/kg dry weight—all the data on Cd level



**Fig. 2.** The North Central Province of Sri Lanka where the chronic renal failure occurs due to cadmium from elevated dietary exposure originated from non-point pollution through cadmium contaminated phosphate fertilizer over the past three decades.

in soil are reported per kg of soil on dry weight basis) (Bandara et al., 2008). These sediments then release  $\text{Cd}^{++}$  into reservoir water (32–57 mg/l) leading to the high level of Cd in irrigation and drinking water.

## 2.2. Cadmium in water reservoirs of NCP

The North Central Province where the chronic renal failure (CRF) is prevalent, is spotted with manmade reservoirs arranged in drainage patterns in cascades of small reservoirs that eventually drain into larger reservoirs of water (Bandara et al., 2008). Drainage from the rice fields in the upper section of the cascade carried to the main reservoir downstream is reused as irrigation water. In one of the districts in NCP, namely Anuradhapura alone (Fig. 2). There are 3000 functioning small reservoirs arranged in 280 separate cascades. Bandara et al. (2008) analyzed water sampled from five main reservoirs for dissolved heavy metals, in the villages where a higher level of occurrence of CRF with, over 5.6% of the farmers were proteinuric, was observed and reported elevated levels of cadmium (Cd), iron (Fe) and lead (Pb) compared to copper (Cu), manganese (Mn) and zinc (Zn) that are present in non-significant

**Table 1**

Mean dissolved heavy metal concentration in waters of reservoirs of NCP, Sri Lanka.

Metal	MCL	Mean concentration (mg/l)				
		1	2	3	4	5
Cd	0.003	0.05 b	0.04 c	0.06 a	0.06 a	0.03 d
Co	N/A	0.22 a	0.14 ab	0.04 c	0.15 ab	0.14 b
Cr	0.05	–	–	–	–	–
Cu	1.00	0.02 ab	0.02 ab	0.03 a	0.02 c	0.02 bc
Fe	0.30	0.20 c	0.79 b	0.47 bc	0.63 bc	1.28 a
Mn	0.05	–	0.18	–	–	–
Pb	0.01	0.03 a	0.01 bc	0.02 ab	0.03 a	–
Zn	2.00	0.10 a	0.10 a	0.06 a	0.11 a	0.10 a

1–4 are the sampled reservoirs in NCP.

1 = Kumbichchankulama, 2 = Alankulama, 3 = Thuruwila, 4 = Karapikkada, 5 = Ullukkulama; MCL = maximum contamination level defined by EPA for drinking water.

Data are mean values of 30 samples for each sampling site.

Values followed by the same letters (a, b, c) are not significantly different at  $P = 0.05$  based on *t* test.

Data from Bandara et al. (2008).

concentrations. The dissolved Cd in reservoir waters ranged from 0.03 to 0.06 mg/l which is a 10–20 fold increase over maximum contamination level (0.003 mg/l) defined by the WHO for drinking water (Table 1). No arsenic (As) or chromium (Cr) was detected at the detection limit 0.015  $\mu\text{g/l}$  used with the Graphite furnace GBC-GF 30000. In a subsequent analysis of further samples of drinking water and irrigation water in NCP, namely in CRF patients' domestic environment of Anuradhapura, Madawachchiya, Pollonnaruwa and Medirigiriya, done by the authors, as described by Bandara et al. (2008), it was observed that all sources of water were contaminated with cadmium and the main source for all supplies is reservoir water (Table 2).

The mean annual rainfall of 1450 mm is received in NCP in a very short period of 4 months and all the reservoirs in the NCP are fed with runoff water from rice fields. The total annual run off from 75,361 ha of rice fields, the mean total extent of rice sown per year and the rest of the catchment area in NCP, is  $2.55 \times 10^6$  ha m (hectare meter). The quantity of sediments brought in by runoff during the cropping season is very heavy. When reservoir bottom sediments were analyzed for heavy metals (Cd, Co, Cr, Cu, Fe, Mn, Pb and Zn), nephrotoxic elements Cd and Pb were detected at very higher level ranging from 1.78 to 2.45 mg/kg of soil (Bandara et al., 2008). Premarathne et al. (2005) reported the mean level of Cd in uncultivated soil in Sri Lanka as 0.39–0.51 mg/kg (Table 1). The Cd content in the soils on the periphery of reservoirs ranges from 0.56 to 1.05 mg/kg. When these reservoirs are at spill level, this area is usually submerged due to input from surface run-off during the rainy season. The bioavailability of heavy metals is affected by soil pH, soil organic matter, cation exchange capacity of the soil, other cations in the soil solution, oxidation and reduction reactions, their ability to form soluble complexes and the impact of soil microflora. Although Cd is highly mobile under acidic conditions, soil pH in the

**Table 2**

Cadmium content  $\mu\text{g/l}$  in random samples ( $n = 50$ ) of water collected from CRF confirmed patients' homes from NCP.

Water	Range	Geometric mean	GSD
Irrigation/reservoir	0.08–29.14	3.174	4.658
Shallow well	0.205–187	6.931	4.747
Agro well <sup>a</sup>	2.72–38.8	11.18	2.782
Pipe borne	0.88–10.38	2.274	1.853
Tube well	1.7–33.66	3.852	2.895

CRF = chronic renal failure, GSD = geometric standard deviation.

<sup>a</sup> Agro wells are shallow dug wells with a mean depth 4.3 m and mean diameter 6 m dug within the paddy (rice) command area. Agro wells are used for the irrigation of upland crops using pumps (Kikuchi et al., 2003).

NCP is neutral to alkaline. Thus unlike in the upcountry tea soils which are rich in organic matter where the pH is around 4.5, the mobility of Cd in NCP soil is low. The  $K_d$ , the ratio of metal concentration in soil to metal concentration in water is determined by the soil pH. The  $K_d$  values of Cd at soil pH 4.5–9.0 is 1.3–26.8 (Bates and Sharp, 1983). However, in the bottom sediments of NCP reservoirs which are under reducing conditions, the solubility of Cd is high especially under the prevailing higher level of  $F^-$  and  $Cl^-$  content in water. The fluoride content in NCP is in the range of 1–3 mg/l and in certain areas of NCP it is the highest in Sri Lanka having more than 3 mg/l fluoride in ground water. In Medawachchiya where highest CRF occurrence is reported, fluoride level in ground water is 700  $\mu\text{g/l}$ . Most NCP ground water contains high level of calcium (in CRF region it ranges 208–220  $\mu\text{g/l}$ ) and the chloride content is more than 2000 mg/l (Dissanayake and Weerasooriya, 1985). Since cadmium is retained in soil by exchange reactions in the presence of cations,  $Ca^{++}$  compete better than  $Cd^{++}$  for adsorption sites in soil, resulting in more  $Cd^{++}$  in water. These environmental conditions in reservoirs of NCP and the groundwater favor more mobile  $Cd^{++}$ . Ariyasinghe (2007) observed that the Cd tolerant bacterium *Sphingomonas macrogoltabida* isolated from Thuruwila reservoir in Anuradhapura of NCP, favors release of cadmium trapped in clay fraction or conversion of colloidal cadmium to exchangeable cadmium. The plant transfer coefficient of cadmium is known to be higher than other nephrotoxic heavy metals such as lead (Lehoczyk et al., 2006).

### 3. Cadmium in food

In a WHO sponsored study, using the methodology described by Bandara et al. (2008), we analyzed the Cd contents of food items routinely used by the CRF patients in Anuradhapura, Madawachchiya, Medirigiriya and Pollonnaruwa area. The mean cadmium concentrations (mg Cd/kg) are reported in Table 3. The maximum permissible level of Cd recommended by Codex (2009), for polished rice grain is 0.4 mg/kg. The maximum value obtained in rice samples collected from CRF patients' rice fields in NCP in the recent study was 0.0925 mg/kg (on dry weight basis) of rice. Therefore the total amount of cadmium accumulated over a long period of time due to elevated dietary intake appears to be detrimental. It

**Table 3**

Cadmium content in  $\mu\text{g/kg}$  (ww basis) in food items collected from randomly selected patients homes and their domestic environment.

Food item	Range ( $\mu\text{g/kg}$ )	Mean ( $\mu\text{g/kg}$ )	SD ( $\mu\text{g/kg}$ )
Rice	1.7–92.5	23.356	22.877
Pulses ( <i>Vigna radiata</i> )	2.1–99.2	31.774	28.047
Tilapia ( <i>O. niloticus</i> )	0.5–90.7	21.763	25.972
Lula ( <i>Channa striata</i> )	1.2–114.4	20.243	36.361
Lotus ( <i>N. nucifera</i> )	2.3–271.3	46.407	71.548
Foliar vegetables	1.6–96.5	23.795	29.415
Milk			
	Range ( $\mu\text{g/l}$ )	Mean ( $\mu\text{g/l}$ )	SD ( $\mu\text{g/l}$ )
Breast milk	0.52–75.32	18.235	20.74
Cows milk	0.12–84.48	14.01	20.90
Buffalo milk	57.1–82.28	69.63	14.15

is more relevant and meaningful to discuss total dietary exposure of the exposed population based on the weekly intake (WI) of cadmium as proposed by Satarug et al. (2000). Bandara et al. (2008) discussed in detail the possible greater exposure to cadmium due to cumulative effects of cadmium carried by various components of a rice and curry meal consumed by Sri Lankans, though rice or fish alone will not elevate the Cd level above the Codex committee recommendations. The provisional tolerable weekly intake (PTWI) recommended by Codex (2009) is 0.007 mg/kg bw. The WI based on recently analyzed data especially breast milk collected from breast feeding mothers living at homes of CRF patients sampled at random is given in Table 4. It is evident from the data given in Table 4 that the WI of Cd is in excess of 7  $\mu\text{g/kg}$  at all age groups though the actual intake of Cd at younger ages is higher. Satarug et al. (2010) however, raised concern about validity of the current safe levels recommended by Codex, with the existing high tendency of environmental exposure. This is due to the overall elevated level of Cd in all food items including breast milk due to wider contamination that has existed through non-point pollution of the whole agricultural region by agricultural inputs. The mean cadmium content in pasture was 0.02789 mg Cd/kg with a range 0.0023–0.0872 mg Cd/kg and S.D. of mean. = 0.0239. We observed that milk of freely grazing buffalo had 57.16–82.28  $\mu\text{g Cd/l}$ . In our field studies we observed that the prevalence of the 5th stage of CRF was common in the age group of 40–60 years in the very early

**Table 4**  
Provisional tolerable weekly intake (PTWI) of cadmium as Cd  $\mu\text{g/kg}$  body weight from most common individual component of diet consumed and as an integrated total meal in comparison to breast milk fed to young infants.

	Age groups (years)					
	Infant	4–5	14	20–29	30–39	40–49
Body weight (kg) <sup>a</sup>	10	16.2	42.4	56.2	57.8	59.3
Daily rice intake (kg) <sup>b</sup>	0	0.19	0.38	0.38	0.38	0.38
Daily fish intake (kg) <sup>b</sup>	0	0.068	0.14	0.14	0.14	0.14
Daily pulses intake (kg) <sup>c</sup>	0	0.032	0.032	0.032	0.032	0.032
Daily milk intake (l) <sup>d</sup>	0.961	0.25	0.25	e	e	e
Weekly intake of Cd $\mu\text{g/kg}$ bw						
WI rice		7.553	5.772	4.355	4.234	4.127
WI fish		2.644	2.081	1.569	1.526	1.487
WI pulse		1.378	0.523	0.395	0.384	0.374
WI cow's milk		9.126	3.487	e	e	e
WI breast milk	48.72					
Total meal WI Cd $\mu\text{g/kg}$ bw <sup>f</sup>	48.72	20.701	11.863	6.319	6.144	5.988

<sup>a</sup> Age group and body weight; Simmons et al. (2005).

<sup>b</sup> FAO (2006).

<sup>c</sup> Based on data obtained by authors on food habits of NCP for this study.

<sup>d</sup> Daily milk intake by infants at body weight of 10.4 kg at 12 months of age (Heird, 2007). WI = weekly intake of cadmium in  $\mu\text{g/kg}$  BW estimated based on the total weekly intake of most common components of a rice staple in NCP, namely rice, fresh water fish, pulses and the potential extreme exposure to Cd based on Cd content: rice 0.092 mg/kg; fish 0.09 mg/kg; pulses 0.099 mg/kg; cow's milk 0.0844 mg/l; breast milk 0.0753 mg/l. Cadmium intakes through vegetables are not used in the estimate due to variation in the Cd availability for absorption in plant material containing fiber.

<sup>e</sup> In Sri Lanka consumption of fresh cow's milk is negligible after passing the teens, therefore in the groups marked by asterisk Cd intake through milk is not estimated.

<sup>f</sup> Total weekly intake was estimated by summing up the Cd intake by a usual meal of rice, fish and pulses in a week.

stages of reporting of CRF incidence in 2000–2002. In 2006–2008 this condition was more common within the age group of 35–45 years. In most recent sampling it was apparent that stage 5 is shifting down to younger patients in the age group of 25–35 years. CRF is now being reported among 15 years and younger age groups. Data demonstrate that the epidemic is shifting to lower age groups. Based on the analysis of local agricultural chemical inputs it was observed that agricultural inputs contaminate a wide area. Among these the surfactant of the herbicide (bispiribac sodium) commonly applied to rice field had a content of 0.0045–0.0615 mg Cd/l) and common surfactant detergent used in pesticide formulations had a Cd content of 3.12 µg/l. Since there is no zinc mining industry or natural cadmium contamination or any industry using cadmium in the NCP region, the pollution of the aquatic resources and farm lands is apparently only by the agricultural practices as non-point pollution.

### 3.1. Cadmium in food produced in the aquatic environment

The heavy metal contamination in the most common food crop grown under lowland condition in the region where CRF is prevalent, namely rice and *Nelumbo nucifera* (Lotus) rhizomes were reported to be significantly higher (Bandara et al., 2008). The cadmium content in rice grains collected from the farms of CRF patients in the NCP ranged from 0.001 to 0.194 mg/kg dry weight with a mean value of  $0.0404 \pm 0.0196$  mg/kg compared to a Sri Lankan background value 0.001 mg/kg. Rhizomes of 120-day-old *N. nucifera* stored seven heavy metals. Bandara et al. (2008) reported a mean concentration of 252.82 mg Cd, 237.73 mg Co, 47.86 mg Cu, 7975.0 mg Fe, 579.44 mg Mn, 16.32 mg Pb and 1461.79 mg Zn per kg of rhizome. In this region the aquatic environment provides not only main plant based food but also the fresh water fish Tilapia (*Oreochromis niloticus*) as a protein source. Cadmium content in fish raised in fresh water reservoirs in the region significantly influenced the total dietary cadmium (Bandara et al., 2008). The estimated weekly intake of Cd from Tilapia and rice, containing 0.325 mg Cd/kg and 0.425 mg Cd/kg, respectively, fish collected from Thuruwila reservoir near Anuradhapura carrying 0.425 mg of Cd/kg and with a rice staple containing 0.194 mg Cd/kg (dw) varied from 28.39 µg/kg body weight in age group of 4–5 years and 15.48 µg/kg body weight in the age group of 40–49 years. In our subsequent studies on Cd residues in fish Tilapia and Lula (*Channa striata*) where samples were collected from fish landed from reservoirs near patients' houses, it was observed that the Cd content ranged 0.5–90.7 µg/kg with a mean of 21.8 µg/kg in herbivorous Tilapia compared to carnivorous snakehead *C. striata* (Lula) with a Cd content of 1.2–114.4 µg/kg. Lula is a solitary, territorial, ambush feeder which consumes mostly worms, prawns, frogs, and especially other fishes. The young fry feed on algae and protozoans, while juveniles feed on small crustaceans. But the adults are highly carnivorous suggesting the potential biomagnifications of any contaminant in the reservoir.

## 4. Source of cadmium

The NCP is the traditional agricultural area of Sri Lanka which has been producing all staple requirements in a sustainable manner during the ancient "Rajarata Civilization" (Rajarata = Ancient Kingdom) utilizing man-made irrigation systems based on 4000 small reservoirs arranged in 250 cascades developed during the reign of King Parakrama Bahu (1153–1186 AD). Though detailed historical records of Sri Lanka are available in the Ancient Chronicle of Sri Lanka, The Mahawamsa (Turnour, 1837), which reports historical events from 6th century BC to 4th century AD in 37 chapters, there are no records of epidemic or deaths due to chronic renal failure or

any large scale migration of population away from Anuradhapura or Polonnaruwa. Irrigation system used today in NCP is the renovated version of the ancient one, which recirculates drainage water from rice fields. We observed that the mean Cd levels in uncultivated soil in Anuradhapura district and Polonnaruwa district of NCP are  $0.023 \pm 0.014$  and  $0.0052 \pm 0.0043$  mg/kg, respectively. The mean Cd content in cultivated soil applied with TSP in Anuradhapura is  $0.1104 \pm 0.186$  and in Polonnaruwa  $0.0159 \pm 0.005$  mg/kg. The soils of NCP are not naturally high in Cd but Cd is added to soil through recently-adopted agricultural practices.

The main agrochemical that adds cadmium to agricultural fields is the TSP or Rock Phosphates. The Cd concentrations detected in TSP used in rice fields ranged from 23.50 to 71.74 mg/kg (Bandara et al., 2008). The use of NPK, the components in a fertilizer mixture: nitrogen (N), phosphorus pentoxide (P), and potassium oxide (K) containing fertilizer in rice cultivation increased with the introduction of new high-yielding improved varieties with the onset of the Green Revolution in 1971. The amount of fertilizer used to cultivate high-fertilizer-responsive rice varieties in 1975 was 74,000 Mt, more than double that used in 1970 (32,000 Mt). Fertilizer use has increased spectacularly with an annual growth rate of 3.5%. The estimated upper level of Cd that could be in the rice-cascade reservoir environment since 1973 is 68.9 Mt based on extreme level of Cd contamination, that is 71.74 mg Cd/kg of TSP (Bandara, 2007).

### 4.1. Health impact

CRF patients in the North Central Province of Sri Lanka are proteinuric with a mean 24 h urine protein excretion of 0.734 g/l (range 0.02–6.5 g/l). It was observed that 45.6% of the patients with persistent proteinuria had early renal disease. Their creatinine clearance (Cr.cl) values were >60 ml/min and 35% of the population had <30 ml/min with late stage of CRF. The mean Cr.cl value of the Madawachchiya, NCP population was 206 ml/min with a wider range of 1.3–1161 ml/min (Athuraliya et al., 2003). Abuelo (1995) defined Cr.cl values for renal failure as follows. 50 ml/min with established norms for normal adult male Cr.cl = 90–139 ml/min and for female with a Cr.cl = 80–125 ml/min. Tubular interstitial renal dysfunction was observed among the CRF patients. The ultrasonography of the kidneys of the patients reported a mean bipolar length of 8.3 cm with a standard deviation of the mean 1.4 cm. The biopsy reports of Madawachchiya patients in 2007 revealed that endocytosis and proximal tubular sclerosis were predominant but no glomerular renal dysfunction was observed, suggesting a potential involvement of chronic exposure to cadmium. Friberg et al. (1986) reported similar effects after long-term accumulation of Cd in the kidney. Female farmers resident in Jinzu River basin in the Toyama Prefecture, Japan exposed to elevated dietary Cd through consumption of high-Cd rice grown with polluted irrigation water developed Itai-itai disease characterized by renal tubular dysfunction, osteomalacia and anemia (Yamagata and Shigematsu, 1970; Aoshima, 1987; Horiguchi et al., 2006; Watanabe et al., 2002). However, osteomalacia was not observed in Sri Lankan patients probably due to higher level of calcium and iron in drinking water in the NCP. It may be that the tropical climate with plenty of sunlight may not favor the occurrence of osteomalacia and the resultant "Ouch-Ouch" condition. The mean urinary cadmium concentration of patients confirmed as CRF with biopsy reports in Anuradhapura is  $7.58 \pm 6.18$  µg Cd/g cr and that of Polonnaruwa is  $5.65 \pm 5.46$  µg Cd/g cr in the age group of 40–60 years (Bandara et al., 2008). An endemic form of CRF emerged in 2002 in the major farming provinces of Sri Lanka. A 2–3% mean prevalence is reported as background, the prevalence exceeds 10% in North Central Province and North Western Province of Sri Lanka, the traditional farming areas of lowland rice. The number of hospital-reported deaths due to CRF is 300–600 annually; however the total

number is ~1400 per year. In the North Western Province where the CRF has been recently reported, the death rate is 50–60 per year (Gunewardena, 2008). Disease is common among lowland rice cultivators and predominantly among young farmers with a male to female ratio of 4:1 (Gunewardena, 2008). Goonewardena et al. (2004) reported that the transitional cell carcinoma (TCC) accounted for 93.4% of primary bladder cancer in Sri Lanka. Exposure to elevated dietary Cd or cigarette smoking is known to cause the TCC (Kellen et al., 2009; Sens et al., 2004; Somji et al., 2006).

## 5. Conclusion

Cadmium toxicity seems to be visible only in NCP and in the adjoining North Western Province where the fluoride content of drinking water is as high as 1–3 ppm. It appears that the cadmium absorption through the gut via divalent metal transporters is facilitated by fluoride as an efficient modifying factor, which needs further study that may assist in mitigation of the situation. It is now known that most human exposure to Cd comes from agriculture which raises the dietary Cd (Satarug et al., 2000) in addition to smoking which is a known factor determining development of bladder cancer (TCC) in Sri Lanka. In Sri Lanka Goonewardena et al. (2004) reported that the, male preponderance in TCC is significant, with a very high male to female ratio of approximately 6:1. Gender differences in cigarette smoking, in Sri Lanka showed that 54% of males and 0.8% of females were smokers (WHO, 1997).

Cd pollution is originated from contaminated phosphate fertilizer used in agriculture (Loganathan and Hedley, 1997). Therefore it is absolutely imperative that universal standards are established for Cd levels in agrochemicals to prevent exposure of more vulnerable farming community to premature death due to CRF through exposure to elevated dietary cadmium.

## Conflict of interest

No conflict of interest among all the authors involved in this minireview.

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