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158

Review of Literature on Chronic Kidney Disease of Unknown Etiology (CKDu) in Sri Lanka

Andrew Noble, Priyane Amerasinghe, Herath Manthrilake and
Sutharsiny Arasalingam



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IWMI Working Paper 158

**Review of Literature on Chronic Kidney Disease of Unknown
Etiology (CKDu) in Sri Lanka**

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Noble, A.; Amerasinghe, P.; Manthrithilake, H.; Arasalingam, S. 2014. *Review of literature on chronic kidney disease of unknown etiology (CKDu) in Sri Lanka*. Colombo, Sri Lanka: International Water Management Institute (IWMI). 41p. (IWMI Working Paper 158). doi: 10.5337/2014.206

/ kidney diseases / chronic course / aetiology / water quality / drinking water / groundwater / contamination / arsenic / toxicity / cadmium / phosphates / fluorides / aluminium / agrochemicals / health hazards / food chains / farmers / wells / literature / research / Sri Lanka /

ISSN 2012-5763

e-ISSN 2478-1134

ISBN 978-92-9090-788-6

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Acknowledgements

The authors would like to thank all the people whose work contributed to the content of this paper. In particular, we are grateful to Dr. T. Abeysekara, Consultant Nephrologist and Former Head, Dept. of Nephrology and Transplantation – Teaching Hospital, Kandy; Prof. O. Ileperuma, Department of Chemistry, University of Peradeniya; Prof. R. Chandrajith, Department of Geology, University of Peradeniya; and Mr. S.G.G. Rajkumar, Deputy General Manager, National Water Supply & Drainage Board, Ratmalana.

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Acronyms

Al	Aluminum
As	Arsenic
CKD	Chronic Kidney Disease
CKDu	Chronic Kidney Disease of Unknown Etiology
CP	Central Province
CRF	Chronic Renal Failure
DZ	Dry Zone
EP	Eastern Province
ESRD	End Stage Renal Disease
F	Flouride
GFR	Glomerular Filtration Rate
NCP	North Central Province
NP	Northern Province
NWP	North Western Province
P	Phosphorus
PTWI	Provisional Tolerable Weekly Intake
ROP	Registrar of Pesticides
SABP	Sabaragamuwa Province
SP	Southern Province
SLMA	Sri Lanka Medical Association
TSP	Triple Super Phosphate
UP	Uva Province
UTI	Urinary Tract Infection
WHO	World Health Organization
WP	Western Province

Summary

The issue of chronic kidney disease of unknown etiology (CKDu) dominates the research arena as well as the media; and has raised the specter of determining the causal factor(s) that contribute to its development. There is evidence to support the notion that the majority of the patients diagnosed with CKDu are farmers, and arguments have been presented to suggest the possibility of water resources being the main contributor to the development of the disease. Thus IWMI became interested in exploring these linkages with the chronic kidney disease that is prevalent in some parts of Sri Lanka, especially in the North Central Province.

What we know about the disease:

- CKDu patients are characterized by non-conformation/association to the known risk factors such as diabetes, hypertension or chronic glomerulonephritis. The onset of the disease appears to be asymptomatic, and by the time the patient seeks treatment the kidneys have reached a stage of irreversible damage -- end stage renal disease (ESRD).
- Over the past 12 years numerous studies have been undertaken by a range of institutions in relation to the problem and, as a result, a body of research has been established. They range from hospital cohort and community level studies; water resource studies; assessments of food sources; and studies into possible genetic linkages. Several of these studies have been published in peer-reviewed journals along with a substantial quantity of material in 'grey literature'.
- The disease is predominantly confined to male farmers in the North Central Province (NCP) of Sri Lanka, who are over the age of 40. Patients are predominantly subsistence farmers and / or agricultural laborers. The ratio of male to females affected by the disease ranges from 3:1 to 2.4:1. There is evidence to suggest that the age of patients diagnosed with the disease is gradually lowering (with community screening); suggesting it is occurring even among younger cohorts of the population as well.
- According to current estimates, CKDu appears to be 3-4 times higher in the NCP than that of most other provinces, except the NP. As early as 2002, three times the national average of CKD patients were found in the NCP. It is not clear whether the progressive increase in patients being diagnosed with CKDu with time is due to increased awareness of the disease, improved diagnostic techniques or to an increase in patients manifesting signs of Coda.
- The occurrence of the CKDu has been reported from outside Sri Lanka as well, including India and Central America. A hypothesis that has been put forward as to why the multitude of farmers is predisposed to the disease, is that they undertake strenuous labor under hot climatic conditions that may lead to chronic dehydration and greater/lesser consumption of water. The literature indicates that under these conditions the disease could occur due to an inadequate intake of water that places stress on the kidneys; or people drinking greater amounts of water that may contain the causal agent(s) that affect the kidneys. This would suggest that water and its constituents may in part play a role in the etiology of the disease, a view that is held by several parties investigating this problem in Sri Lanka who we have contacted.

- There is very little supporting evidence to infer aflatoxin contamination as a significant causal factor responsible for the development of the disease in Sri Lanka.
- Arsenic (As) has been implicated, however, all but one of the materials reviewed were in the category of non-peer reviewed publications hence, making it difficult to verify the veracity of these assertions. While elevated levels of (As) are reported to have been measured in groundwater samples collected by groups working on the issue, the strongest endorsement that (As) is not viewed as a candidate for the development of the disease comes from the World Health Organization (WHO). In their study of groundwater samples collected from the areas identified as hotspots for CKDu, arsenic (As) levels were found to be 'normal'. However, a recently published article has implicated (As), and offers heavy metals in conjunction with water quality (hardness of water) as causal factors in the development of the disease. The agro-chemicals that are routinely used in rice production systems have been identified as the source of (As). Since (As) being associated with agro-chemicals has been suggested as the possible source, it is difficult to reconcile why the disease does not afflict all rice growing areas of Sri Lanka, where these chemicals are routinely used in the rice production systems.
- Cadmium (Cd) has been implicated as a causal factor contributing to the disease, and the source of contamination being identified as triple super phosphate (TSP). Elevated levels of Cd were reported in waters from the reservoirs within the Mahaweli diversion scheme, soils, and in a range of foods commonly consumed by rural communities. Cadmium levels measured in soils and rice samples by one of the groups appeared to be elevated, although they were not as high as those measured in Thailand, where known Cd-related kidney disease had been identified. Further studies have questioned the veracity of these results. It is difficult to reconcile the role of Cd in the disease, as TSP use is widespread throughout the agricultural sector in Sri Lanka and elsewhere. One would, therefore, expect to find the incidence of the disease more common throughout Sri Lanka, which is not the case. Hence, it is unlikely that Cd plays a significant role in the development of the disease.
- Toxicity associated with the formation of aluminum (Al) fluoride by the reaction between fluorides in water with the aluminum found in low-quality utensils, which are in wide use in these areas has been suggested as a possible causal factor. Although the usage of low-quality aluminum utensils has been discouraged by the government in CKDu endemic areas, it is not clear whether there is any clinical evidence to support this hypothesis.
- What does appear as a potential causal factor in the development of the disease is, the fluoride (F) in the groundwater and its interaction with other ionic constituents that are present namely, Ca, Na and possibly Mg. There is evidence to suggest that the disease is confined to areas where high levels of F are present in the groundwater, and that it is not the concentration of F per se, but rather the interaction of F with constituent ions in the solution.
- There is a growing body of knowledge that would suggest a genetic link to the problem that predisposes certain individuals to the disease. We are aware that a peer-reviewed article is currently being prepared that supports this hypothesis.

There is evidence to suggest that water quality plays a role in the development of the disease. In discussions with our colleagues in the Water Board, it was revealed that in villages where there

was a high incidence of the disease, the provision of safe drinking water has reversed that situation. However, this has not been verified through controlled studies, but does offer insights into the possible role of water in the development of the disease.

This review was undertaken in response to growing concerns over the occurrence of chronic kidney disease of unknown etiology (CKDu) in Sri Lanka, and the potential role that agriculture and water resources may play as causal factors in the development of the disease. The content describes a review of current published information on CKDu in Sri Lanka; an assessment and commentary on potential environmentally-induced causal factors that have been implicated in the development of the disease, and identifies the gaps in research and recommends potential areas of research where IWMI could contribute to addressing the current impasse.

INTRODUCTION

The endemic occurrence of chronic kidney disease of unknown etiology (CKDu) -- (sometimes referred to as chronic renal failure [CRF]) was first observed in the 1990s, and over the past 15 years the prevalence of the disease within certain geographical locations has increased dramatically. The unique feature of the disease is that, it has no association with the well-known risk factors such as diabetes, hypertension or chronic glomerulonephritis. The onset of the disease appears to be asymptomatic, and by the time patients seek treatment, the kidneys have reached a stage of irreversible damage (end stage renal disease [ESRD]).

A retrospective, descriptive hospital cohort study carried out during the period 2001–2002, indicated that the number of persons with health issues seeking treatment at nephrology clinics in Anuradhapura and Kandy were increasing, and the majority was CKDu patients (Athuraliya et al. 2006). More recent investigations from community-based studies, report significantly higher rates (12.9%) (Jayatilake et al. 2013). To date, the most number of CKDu patients have been reported from three provinces i.e., NCP, UP and EP, with a high prevalence of CKDu observed in the regions of north central Sri Lanka, mainly in DS Divisions of Medawachchiya, Girandurukotte, Kabithigollawa, Padaviya, Medirigiriya, Dehiattakandiya and Nikawewa regions (Figure 1).

The disease appears to mainly affect the proximal tubules and the interstitium giving rise to characteristic, recognizable histopathological and clinical features. Clinically, the disease is characterized by tubular proteinuria, usually β 2-microglobulinuria, and the absence of hypertension and edema. The histological appearance of the disease reveals a tubulointerstitial pathology that can commonly be observed in toxic nephropathies (Athuraliya et al. 2011). To date, there is no unequivocal evidence to recognize the possible environmental causative factors that could lead to nephrotoxin being responsible for the disease (Chandrajith et al. 2011a).

A number of studies report on CKD and CKDu prevalence. The study populations vary widely and, therefore, the interpretations have to be done contextually. In general, CKDu is more prevalent among men (ratio of 3:1) who are typically around the age of 40-60 years, and are engaged in agriculture. Recent personal communications from scientists are pointing to episodic dehydration as a cause that could be a contributing factor for CKDu (farmers undergo episodic dehydration events due to their field activities), and the strong association with lifestyle habits that included smoking and the consumption of illicit liquor and microalbuminuria that is documented (Wanigasuriya et al. 2011).

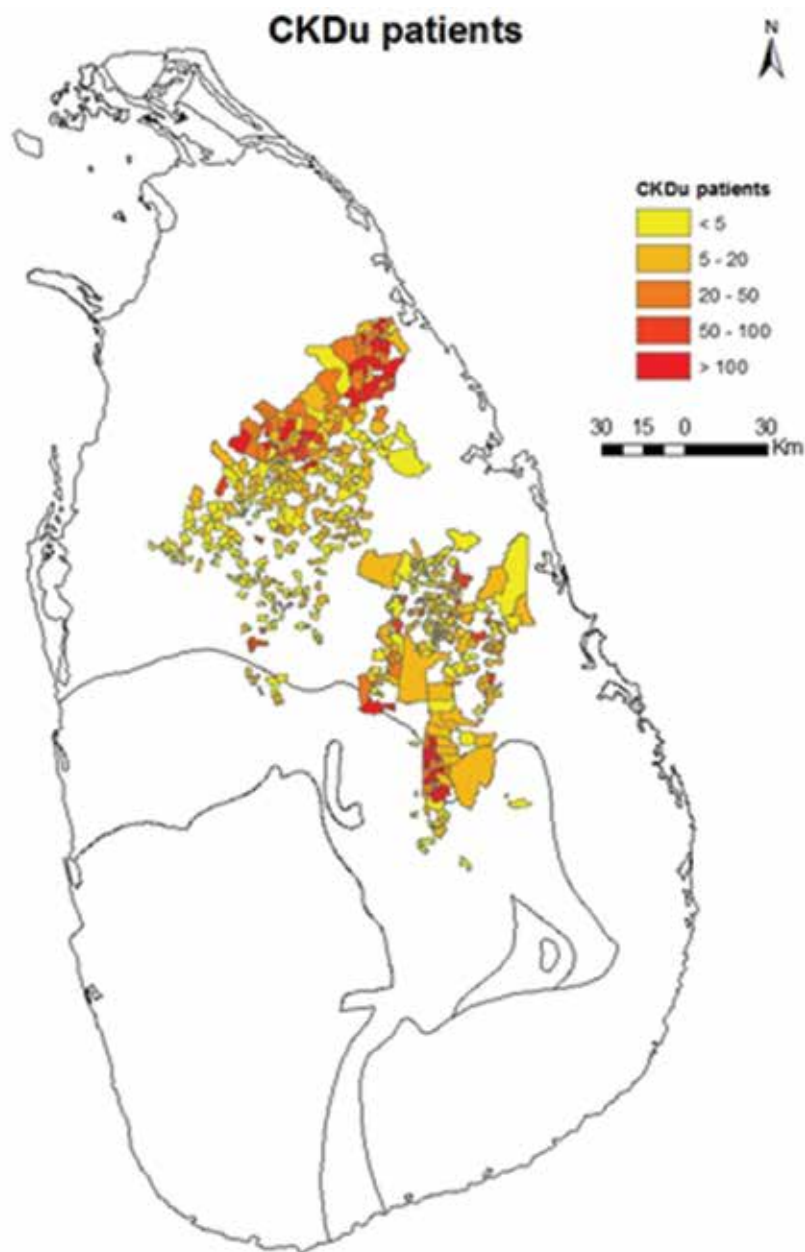
Government statistics indicate over 1,500 deaths due to CKD (Groundviews 2012). Treatment for patients affected by the disease is either through a kidney transplant or dialysis, in the case of the latter treatment has to be carried out at least once a week. However, these treatments are carried out only in specialized hospitals. Twelve clinics in the region have been identified for screening diagnosis and referral. Despite these measures, the number of dialysis machines in the hospitals in the affected districts, are not adequate. Furthermore, the high costs (around LKR 6,000-10,000) for a single dialysis treatment, can be prohibitive for farmers.

Based on the available information, it is estimated that the affected area covers approximately 17,000 km² with a population of approximately 2.5 million, in which, more than 95% live in rural areas. The endemic foci are scattered in a mosaic pattern, with endemic CKDu regions located within a few kilometers from the non-endemic villages (Figure 1). Even within an endemic village, certain households may have had the disease, while neighboring households have had no recorded cases. As the disease has a specific geographical distribution, it is very likely that environmental and/or genetic factors are strongly linked to the etiology and progression of the disease (Chandrajith et al. 2011a). In this respect, the predominant causal factor(s) that have been suggested in the literature that may contribute to the development of the disease, include heavy metals (cadmium [Cd], arsenic [As] and

various nucleotides, including uranium [U]), elevated levels of fluoride (F) in groundwater, the specific composition of groundwater, aluminum (Al), and aflotoxins.

It is worth noting that this issue of chronic kidney disease (CKD) is not confined to Sri Lanka, and that there are reports in the literature that describe similar clinical aetiologies from India (Rao and Pereira 2007), Nicaragua (Torres et al. 2010), Costa Rica (Cerdas 2005) and other Central American states. The reports from Central America cite an increased risk of the disease among agricultural workers, in general, and sugarcane workers, in particular. They have also noted that kidney disease decreases at higher altitudes. Heavy workloads in hot climatic conditions often lead to chronic dehydration, which has emerged as a possible hypothesis in Central America (Callejas et al. 2006). Torres et al. (2010) argue that almost nothing is known about the presence of environmental pollutants in drinking water in the area in which they undertook their studies, and posit that possibly

FIGURE 1. Distribution of CKDu patients reported.



Source: Adapted from Jayasekara et al. 2013

people who work under the hardest conditions sweat more and, as such, consume more water. Thus, inferring that water and its attributes may play a role in the development of the disease.

WHAT DO WE KNOW ABOUT THE DISEASE IN SRI LANKA?

While there is still considerable debate and conjecture over the causal factors contributing to the development of CKDu, there are facts supported by information that provide insights into the disease. These include the following:

- The disease has a higher prevalence in male farmers from the North Central Province of Sri Lanka, who are over the age of 40 years. These patients are predominantly subsistence farmers and / or agricultural laborers. These communities are often poor (income less than LKR 10,000 per month), and are found in areas of the country where poverty is endemic.

There are other attributes that have been reported that may contribute to the disease development, or they could be just a gamut of features commonly associated with the farming population.

- Previous exposure to snake bites, the consumption of illicit liquor, and the use of medicinal preparations associated with Ayurvedic medicine.
- Lack of adequate consumption of liquids during periods of physical work, which results in excessive dehydration that has an effect on the kidneys.
- The chewing of betel leaves with lime and the use of tobacco.
- Malnutrition that is exemplified by low body mass index (BMI) has an impact on the kidneys that predisposes persons to the disease.

An Overview of Medical Evidence Associated with CKDu

The Sri Lanka CKDu citations refer to cases related to around 1,999 of patients receiving treatment at Kandy and Anuradhapura General Hospitals. With the establishment of special nephrology clinics and units within each of the aforementioned hospitals, an increasing trend in the diagnosis of the disease was observed. From 2004-2006, a range of scientists investigated with considerable interest into multiple associations that could shed light on a possible etiologic agent.

The studies to date have utilized hospital cohorts that were classified as CKDu on a mixture of clinical, pathological and chemical characteristics, which appears to have evolved with field experiences. Community-based studies have also been undertaken across provinces to understand the geographical distribution of the disease.

By 2008, the CKDu problem received national prominence and the Government of Sri Lanka invited the WHO to look into the problem through a systematic study, referred to as the National Research Program that was funded by the National Science Foundation and the WHO. The results of this study are now available in the public domain (Jayatilake et al. 2013).

Criteria Used in Classifying the Disease

In reading clinical articles that are in the public domain, a definitive classification or definition of CKDu is often not cited. It appears that cases are classified based on individual clinicians working in the area and, it is not clear, whether they are using the same criteria across clinics. Criteria that have been used to classify patients diagnosed with CKDu are highlighted below.

Criteria used for classification of CKDu patients by consultants, at patient care/dialysis clinics as at 2012 (Personal communication, Tilak Abeysekera 2012).

1. Exclude all known etiologic agents - diabetes, snake bites, leptospirosis, stone diseases etc.
2. Urine test - proteinuria less than 300 mg/L, during a 24-hour period – three samples at least
3. Urine full report – should have no red cells
4. Ultra scan – increased echogenicity
5. Biopsy – tubular interstitial pathology, small size
6. Living in a CKDu endemic area, for more than 5 years

Characterization of a chronic kidney disease (CKD) patient (Athuraliya et al. 2011). Chronic kidney disease (CKD) is diagnosed based on the definition of the Kidney Disease Quality Outcome Initiative (KDQOI) of the National Kidney Foundation, USA. It is a clinical disease that is diagnosed based on structural and/or functional abnormalities of the kidney persisting for 3 or more months, irrespective of the cause of the disease. The functional damage, which is assessed by the measurement of the glomerular filtration rate (GFR), is classified into five stages. Stages one and two, with a GFR (measured by creatinine clearance) of >90 ml/min and evidence of structural changes, which are considered as early symptoms of the disease. GFR <60 ml/min is categorized as stage-three CKD, irrespective of structural changes. As per the KDQOI, any structural kidney damage, evidenced by biomarkers; urinary proteinuria and/or imaging abnormalities, with or without decreased GFR, are also considered as features of CKD. Stage four and five are late stages of the disease with a GFR of <30 and <15 ml/min, respectively (Kopple 2001). CKD can bring about structural and functional changes.

CKDu case definition - Health Ministry Circular.¹ No past history or current treatment for diabetes mellitus and chronic and/or severe hypertension, snake bites, urological disease of known etiology or glomerulonephritis.

Normal HbA1C² (Glycated Hemoglobin) < 6.5%

Blood Pressure at < 160/100 mm Hg or 140/90 mm Hg on up to two antihypertensive agents³

CKDu stages one to four are based on National Kidney Disease Outcome Quality Initiative defined previously, but modified for logistic and financial reasons.

Community screening for CKDu patients. At a field level, studies have utilized the dip stick method for the detection of proteinuria (Athuraliya et al. 2011) and albumin creatinine ratio (30 mg/g) -- (ACR micro-albuminuria - WHO study), from which early signs of CKD could be detected. The sensitivity levels appear to be different between the two tests. Experiences suggest that the proteinuria test can pick up 8-9% of the cases, whereas micro-albuminuria test appears to pick up around 20% of the cases. 'Light dependent resister micro-albumin gel filtration method' was used for initial screening for micro-albuminuria and reconfirmed by the *Micral* strip test (Wanigasuriya et al. 2011).

¹ http://www.whosrilanka.org/LinkFiles/WHO_Sri_Lanka_Home_Page_CKD_Leaflet_Feb_2010.pdf.

² A form of hemoglobin that is measured primarily to identify the average plasma glucose concentration over prolonged periods of time.

³ A patient can be on treatment for hypertension, when late stage cases present, they will be under treatment for hypertension.

Patient Cohorts Described in the Scientific Literature

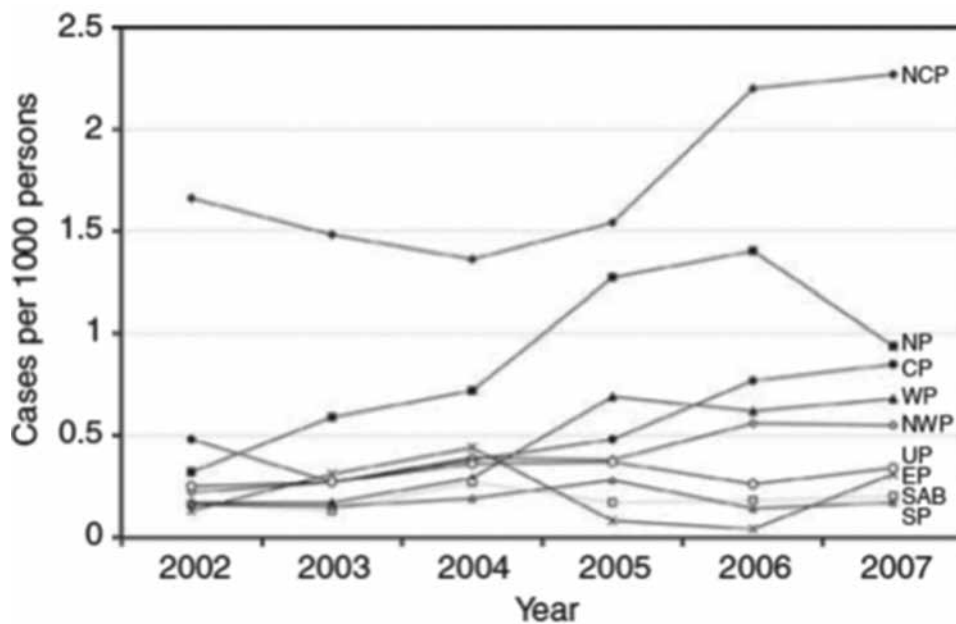
Patients seeking treatment at government district/base hospitals – country-wide data:

Athuraliya et al. 2011 described the development of the disease over the period 2002–2007, using data collected from the epidemiology unit of the Ministry of Health (Figure 2). It includes all types of CKD patients registered at hospitals, and does not distinguish between the known and unknown aetiologies, (i.e., CKD from CKDu) of the disease.

It is clear from Figure 2, that the prevalence of the CKD in the North Central Province (NCP) is three to four times higher than that of most other provinces, except the NP. As early as 2002, three times the national average of CKD patients were found in the NCP. It is not clear, whether the progressive increase in patients being diagnosed with CKD with time is due to increased awareness of the disease, improved diagnostic techniques or to an increase in the number of patients manifesting signs of CKD. Taking 2002 as the point at which clinicians became concerned over the incidence of the disease, it would be interesting to go back further in time to see whether there was a point where the incidence of the disease in the NCP was at the same level as that of the other provinces. However, there could be a paucity of information, in the registries that may hinder such a retrospective study.

The prevalence of the disease within a community-based study in sample populations from five provinces is presented in Table 1. The three province (NCP and UP) had the highest percentage of patients with CKD classified as CKDu cases, based on the elimination of diabetes and hypertension being causal factors in the development of the disease, supporting the notion of a geographical preference for the development of CKDu.

FIGURE 2. Cases of chronic kidney (CKD) reported from the main hospitals of each province in Sri Lanka over the period 2002-2007. CKD is defined as eGFR ≤ 60 ml/min per 1.73 m² Ministry of Health 2009. (eGFR is the estimated glomerular filtration rate). The provinces are: CP (Central Province); EP (Eastern Province); NCP (North Central Province); NP (Northern Province); NWP (North West Province); SP (Southern Province); SAB (Sabaragamuwa Province); UP (Uva Province); and WP (Western Province).



Source: Adapted from Athuraliya et al. 2011

Community-based study on CKD. In a study undertaken by Wanigasuriya et al. (2011), exposures to possible risk factors were determined using an interviewer-administered questionnaire among randomly recruited subjects (425 females and 461 males) from selected areas of the NCP. Sulfosalicylic acid and the ‘light dependent resister micro-albumin gel filtration method’ was used for initial screening for micro-albuminuria, and was reconfirmed by the *Micral* strip test. In their previous study, which is a case-control study, being a farmer ($p < 0.001$), using pesticides ($p < 0.001$), drinking well water ($p < 0.001$), having a family history of renal dysfunction ($p = 0.001$), use of ayurvedic treatment ($p < 0.001$) and a history of snake bites ($p < 0.001$) were found to be risk factors for CKDu.

Micro-albuminuria was detected in 6.1% of the females and 8.5% of the males. The following too were detected: smoking ($p < 0.001$), alcohol use ($p = 0.003$), hypertension ($p < 0.001$), diabetes ($p < 0.001$), urinary tract infection (UTI) - ($p = 0.034$) and consumption of water from wells in the fields ($p = 0.025$) were associated with micro-albuminuria. In the binary logistic regression analysis; hypertension, diabetes mellitus, UTI, drinking well water in the fields, smoking and pesticide spraying were found to be significant predictors of micro-albuminuria. The association between micro-albuminuria and consumption of well water suggests an environmental etiology to CKD in the NCP. However, the causative agent has yet to be identified. Nevertheless, there are suggestions that water quality attributes may influence the development of the disease (see later discussion).

As of 2011, 12 government clinics have been established, to specifically take care of patients suffering from CKD. These are at Padaviya, Medawachchiya, Kabithigollaowa, Medirigiriya, Hingurakgoda, Polonnaruwa, Anuradhapura, Girandurukotte, Mahiyangana, Dehiathakandiya, Wilgamuwa/Hettipola and Nikawewa. It is envisaged that patients can receive early treatment without having to travel far distances within the region.

Field studies undertaken by Bandara et al. (2010a) have revealed that the prevalence of the fifth stage of Chronic Renal Failure (CRF) was common in the age group of 40–60 years in the very early stages of reporting of CRF incidence in the years 2000–2002. However, during 2006–2008 the condition was found to be more common within the age group of 35–45 years, and in the most recent samplings it was apparent that stage five is shifting down further to younger patients in the age group of 25–35 years.

TABLE 1. The prevalence of CKDu as shown in community-based studies conducted in five provinces. Data collected over the period 2003-2008.

Province	North Central	North Central	Uva	Central	Southern	Eastern
Region	Medawachchiya	Huruluwewa	Giradurukotte	Yatinuwara	Hambantota	Ampara
Year surveyed	2003	2001, 2005	2006	2004	2008	2008
Sample size	4,107	233	1,345	253	4,023	3,232
CKD prevalence >18 years (%)	3.7	3.2	3.9	3.2	2.53	2.20
Overall population (%)	5	0.2	4.0	3.2	3.49	3.15
CKD with ncertain etiology (%)	84	0	96	0	1	0.75
Diabetes in >18 years (%)	3.4	-	2.1	16.4	4.88	3.66
Hypertension in >18 years (%)	5.2	-	4.5	9.1	6.11	5.57

Source: Chandrajith et al. 2011a

SOME POTENTIAL CAUSAL FACTORS OF CKDU, REPORTED IN THE LITERATURE

Aflotoxins Associated with the Consumption of Stored Grains

The following section describes causal factors that have been identified or suggested as contributing to the development of CKDu. These are not in any order of preference.

The Balkan endemic nephropathy (BEN) has been described as a chronic kidney disease prevalent among settlers along the tributaries of the Danube River in Serbia, Bosnia, Bulgaria and Romania (Stefanovic 1998). First described in 1957, BEN is a slowly progressive tubulo-interstitial disease leading to end-stage renal failure.

This disease has several factors similar to those of renal failure patients from the North Central Province, including the fact, that the disease affects predominantly farmers, a familial aggregation of cases and interstitial nephropathy seen in renal biopsies (Hittarage 2004). One hypothesis considers that mycotoxins ingested in small amounts by individuals in the endemic regions might initiate the process of renal damage. However, it has been identified as a rare condition due to the corona virus EBNV (Uzelac-Keserovi et al. 1999).

Although mycotoxins have been suggested as a factor in CKDu in Sri Lanka, Wanigasuriya et al. (2008) found that it was highly unlikely that mycotoxins of food products could cause nephropathy in the NCP. They assessed 98 randomly selected commonly consumed foods sourced from the NCP of Sri Lanka for ochratoxin a (OA), a naturally occurring mycotoxin with nephrotoxic properties that can contaminate plant food products. They reported that levels of OA found in these foods were below the recommended statutory maximum limit and, as such, were unlikely to be a potential risk factor for nephropathy in the NCP of Sri Lanka. Based on the evidence presented, we are of the opinion that this factor as a causal element in the development of the disease should be considered to be slight.

Arsenic (As) Toxicity

Over the past two decades, the occurrence of high levels of arsenic (As) in drinking water has been recognized as a significant public health issue, which is global in extent. The adverse health effects of (As) depend strongly on the dose and duration of exposure. Specific dermatological effects are characteristic of exposure to (As). These include melanosis coli (pigmentation) and keratosis pilaris (rough, dry common skin lesions); both may be spotted or diffused. Chronic exposure to (As) may also cause reproductive, neurological, cardiovascular, respiratory, hepatic, hematological, and diabetic effects in humans (National Research Council 1999). Ingestion of inorganic arsenic is an established cause of skin, bladder and lung cancers (National Research Council 1999, 2001).

Critical Values of Arsenic (As) in Water and Food

There is still some debate over permissible levels of (As) in food and water sources. In Bangladesh and India (eastern Indo-Gangetic Plain), (As) contamination of groundwater is a significant health issue affecting millions of rural communities. The permissible level that has been prescribed by the Governments of India and Bangladesh for drinking water is 50 µg/L (Mukherjee et al. 2006). The provisional guideline value of 10 µg/L was previously supported by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), with a provisional tolerable weekly intake (PTWI) of 15 µg/kg of body weight, assuming an allocation of 20% to drinking-water. However, JECFA recently re-evaluated arsenic and concluded that the existing PTWI was very close to the lower confidence

limit on the benchmark dose for a 0.5% response (BMDL0.5) calculated from epidemiological studies (specifically for an increased risk of lung cancer) and, therefore, was no longer appropriate. Hence, the PTWI was withdrawn (FAO/WHO 2011a, b).

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that for certain regions of the world where concentrations of inorganic arsenic in drinking-water exceeded 50–100 µg/L, some epidemiological studies provided evidence of drinking such water having adverse effects on humans. There are other areas where arsenic concentrations in water are elevated (e.g., above the WHO guideline value of 10 µg/L), but are less than 50 µg/L (Mukherjee et al. 2006). In these circumstances, there is a possibility that adverse effects could occur as a result of exposure to inorganic arsenic from water and food, but these would be at a low incidence that would be difficult to detect in epidemiological studies. In Bangladesh alone, there are significant numbers of tubewells that exceed both the WHO guideline of 10 µg/L and the Bangladesh permissible limit of 50 µg/L, with concentrations of arsenic ranging from 50 to 3,200 µg/L (British Geological Survey 1999, 2001). In a study by Mukherjee et al. (2006) arsenical skin lesions were reported in 42 of 150 adults and 9 of 58 children examined. About 75% of people had arsenic in hair, which was above the toxic threshold level 1,000 µg/kg (n = 150).

Fish and meat are the main sources of dietary intake of arsenic (Gartrell et al. 1982) levels ranging from 0.4 to 118 mg/kg have been reported in marine fish sold for human consumption, and concentrations of (As) in meat and poultry can be as high as 0.44 mg/kg (Health and Welfare Canada 1983).

Evidence of Arsenic (As) Contamination in Sri Lanka

In a clinical study of 13 cases of polyneuropathy connected with arsenic (As) poisoning in Sri Lanka, Senanayake et al. (1972) found mee's (transverse white bands across fingernails) to be a constant feature at least 6 weeks after the onset of initial symptoms. In seven of the cases, the source of arsenic was contaminated well-water; four others had a long history of consuming illicit liquor.

Within Sri Lanka a group of researchers from Sri Lanka's University of Kelaniya and the Rajarata University (for brevity they are referred to as the (As) Group) conducted studies on widespread arsenic contamination of food, drinking water and the soil. The group comprised of the following persons: Prof. Nalin de Silva, Dean Science, University of Kelaniya; Prof. Priyani Paranagama, Head Chemistry University of Kelaniya; Prof. Mala Amarasinghe, Head Botany University of Kelaniya; Dr. Kithsiri Senanayake, Senior Lecturer, University of Kelaniya; Dr. K. Dahanayake, Acting Consultant JMO, DG Hospital, Monaragala; Dr. Channa Jayasumana, Faculty of Medicine, Rajarata University; Dr. Chinthaka Wijewardhane MOIC, Padavi Sripura Hospital; Dr. P. Mahamithawa, Faculty of Medicine, Rajarata University; Dr. L. Rajakaruna, Faculty of Medicine, Rajarata University; Dr. D. Samarasinghe, Karawanella Base Hospital; and Mr. Saranga Fonseka, University of Kelaniya). They have released the results from their studies, which have been undertaken by a research cohort within the institution citing widespread arsenic contamination of drinking-water, food and soil, and have inferred that pesticides/herbicides/and/or groundwater are the sources of contamination (SLMA 2012). However, the details of the methodologies and descriptions study cohorts are not available for comparison. The findings are summarized below:

Dassanayake et al. 2012 states that arsenic-related skin changes were seen in 30 patients of the NCP, however, they were not afflicted with CKDu. This is in stark contrast to reports from other research groups based at the Rajarata University. In the latter case, the research group undertook a study that contained 56 diagnosed CKDu patients and a control group of 62 individuals from the

Padavi Sripura area. Spotty pigmentation was observed on the palms of 42 (75%) and 48 (85.7%) in the soles of CKDu patients. However, similar pigmentation was observed in the palms of 22 (35.4%) and soles of 26 (41.9%) of non-CKDu individuals in the control group (SLMA 2012).

In a an undated report by the (As) group they go further with their assessment of external dermal manifestations of the disease, in which they describe the observed features as evidence of chronic arsenic symptoms within the sample CKDu patients. Their results are presented in tabular form below in Table 2. Based on the greater number of CKDu patients exhibiting signs of chronic (As) poisoning associated with dermal features compared to that of the control group, the authors conclude that (As) is a factor in the development of the disease and that groundwater is the possible source. They also note that *‘individuals of the control group, however, indicate that being inhabitants of the area who use the same water for drinking, have already bio-accumulated (As), nevertheless, to a lesser extent than those who have been diagnosed as CKDu patients, which means that they too will suffer with CKDu with continuous use of (As) contaminated groundwater.’* It is not clear from the report where the sample cohorts were drawn from, their background and the method that was used to construct the two groups. The report does allude to the fact that at least some of those in the control group were accessing drinking-water from the same source as the CKDu cohort. It would have been instructive to have seen a breakdown of the age distribution of the two cohorts with respect to each of the dermal manifestations measure, as this would give some indication of whether there is a time factor in the development of these symptoms in the two groups.

In the (As) group’s abstracts submitted to the SLMA (2012) they conclude that *“this [skin pigmentation] couldn’t be due to CKDu alone as it is present even in individuals who have not been diagnosed to suffer from CKDu,”* clearly contradicting their previous statements. As a follow up to the statement in the SLMA (2012), Jayasumana et al. (2013) indicated that *“more than half the patients (54.4%) exhibited hyper-pigmentation in palms and 49% in soles although prevalence of keratosis was relatively low among them. Furthermore, nearly 10 to 25% of the individuals of control group too manifested similar symptoms. Some individuals in the control group also showed other symptoms manifested in CKDu patients, nevertheless to a lesser degree.”* Again they did not invoke these well recognized physical features of (As) toxicity as supportive evidence of the same in their studies. It is assumed that they were using the same data sets from the report of the (As) Group.

In discussions with clinicians from the University of Peradeniya, the results from an assessment of patients that have been diagnosed with CKDu by dermatologists concluded that there was no evidence to indicate the presence of pigmentation and keratosis of the skin, nor evidence of mee’s that are common to persons suffering from (As) toxicity. There is no agreement among clinicians that the pigmentations were due to (As) exposure.

TABLE 2. Percentage of dermal manifestation of chronic (As) poisoning symptoms observed in CKDu patients and with individuals on the control group.

Dermal manifestation	Number of patients (n = 125)	% patients	Number of individuals in the control group (n = 180)	% control
Hyper-pigmentation of palms	68	54.4	34	18.8
Hyper-pigmentation of soles	49	39.2	26	14.4
Keratosis of palms	29	23.2	19	10.5
Keratosis of soles	22	17.6	15	8.3

Source: Jayasumana et al. 2013

Arsenic concentrations in hair and urine samples from CKDu patients in Padaviya, Sripura and Welioya divisional secretarial areas were compared to non-CKDu individuals (SLMA 2012). Sample sizes were 100 and 102 for CKDu and non-CKDu individuals, respectively (Table 3).

The authors indicate that 59% and 69% of CKDu patients had hair and urine samples, respectively, that exceeded permissible toxic levels. In the case of the non-CKDu group these values were 34.3 and 28.4%, respectively. While measured values in each of the two cohorts would suggest a higher number of patients in the CKDu group exceeding legitimate toxicity levels, there are almost a third of the control group that have concentrations that exceed the critical values. It would be instructive to look at the distribution by age class of these measured concentrations within the sample group.

In a report put out by the (As) Group, the concentration of (As) in urine samples from the aforementioned two cohorts have been measured (Figure 3).

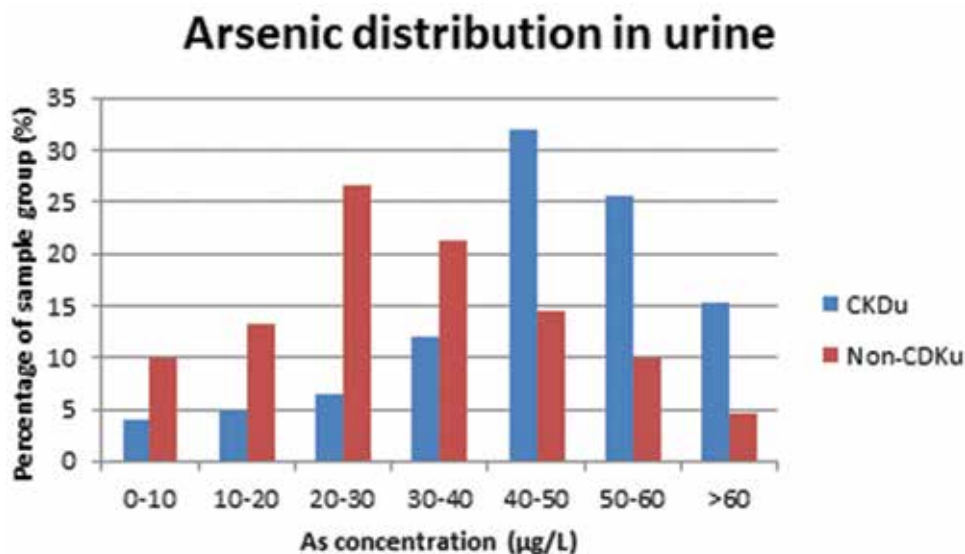
It is assumed that the levels of (As) in urine are associated with the entire volume collected and not associated with the measured creatinine. They have indicated that levels exceeding 35 µg/L would be considered as evidence of toxicity, which from this data set would suggest that the CKDu sample group had a higher proportion of patients exhibiting toxic levels when compared to the non-CKDu group.

TABLE 3. Tabulated data on arsenic concentrations in the hair and urine samples of two cohorts of CKDu patients and non-CKDu patients.

Sample Group	Hair (mg/kg)	Urine (µg/L)
CKDu	0.72±0.20 – 8.75±1.06	18.6±5.8 – 94.50±10.2
Non-CKDu	0.12±0.08 – 4.35±0.92	9.0±3.2 – 44.35±7.9
Toxic levels	1.0	35.0

Source: SLMA 2012

FIGURE 3. Arsenic distribution in the urine of CKDu (n = 125) patients and non-CKDu (n = 180) cohorts.



Source: Data adapted from Jayasumana et al. (2013)

In a WHO memo mission report dated February 13, 2012 associated with the National Research Program initiated by the WHO and Ministry of Health, indicates that in the analysis of 469 cases of CKDu, 63% of patients had urine (As) levels above 21 $\mu\text{g/g}$ creatinine. Urine (As) levels above 21 $\mu\text{g/g}$ creatinine have been shown to cause changes in kidney tissue that leads to chronic kidney diseases (WHO n.d.). In addition, the report highlighted the results from hair and nail samples collected for (As) analysis. They found that in a survey of people living in the NCP that included CKDu patients, 90% had (As) levels in hair samples that were higher than those observed in developed countries (0.02 $\mu\text{g/g}$ or 0.02mg/kg), and that 94% had (As) levels in nails that were higher than those observed in developed countries ($>0.03 \mu\text{g/g}$ or $>0.03 \text{ mg/kg}$). It is of note that the authors do not indicate whether these levels of arsenic were sufficient enough to cause damage to the kidneys or whether they exceeded permissible levels. The toxicity value as stated in Table 3 for hair is 1 mg/kg, which is 50 times higher than the value of 0.02 mg/kg as reported as being commonly observed in the hair of cohorts from developed countries. Without the actual values of (As) that were measured in this WHO assessment, it is difficult to assess the degree of toxicity.

In discussions with the Peradeniya CDKu group, it was revealed that they have taken hair samples from two cohorts, those affected by CKDu and those that are not, for analysis of (As). The samples are being processed in Japan in collaboration with Kyoto University (Personal communication, Tilak Abeysekara 2012).

An interesting article on the analysis of (As) in water samples is presented by a group from the Kelaniya University. The group used two methods for detecting (As) in samples, namely, AAS with Hydride Generator (HGAAS) and Graphite Furnace (GFAAS). Both ground and surface waters were collected from CKDu endemic areas as well as from non-CKDu areas as a control. The total number of samples analyzed was 88. Differences were found between the two methods of analysis, with GFAAS giving consistent and significantly high measured values compared to the HGAAS method. Arsenic in a sample of hard water (410 mg/L) when measured with GFAAS and HGAAS gave values of $40.32 \pm 1.67 \mu\text{g/L}$ and $0.6 \pm 0.21 \mu\text{g/L}$, respectively. The authors suggest that the differences between the two methods may be associated with the hardness of the water creating stable hydrates that are not readily ionized in aqueous solutions. One would assume that the proponents could have assessed the validity of their hypothesis by acidifying the water samples through the addition of HNO_3 , and then reanalyzing them using the two approaches.

The WHO (2011) recommends the following methods for the determination of (As): *A silver diethyldithiocarbamate spectrophotometric method is available for the determination of arsenic; the detection limit is about 1 $\mu\text{g/L}$ (ISO 1982). Graphite furnace atomic absorption spectroscopy, hydride generation atomic absorption spectrophotometry and inductively coupled plasma mass spectrometry (ICP-MS) are more sensitive. High-pressure liquid chromatography in combination with ICP-MS can also be used to determine various arsenic species (Irgolic 1982).*

The authors do not report any other information concerning (As) levels in the two sampling groups, nor give any indication of the highest and lowest levels that were measured. Furthermore, the level that they report ($40.32 \pm 1.67 \mu\text{g/L}$) exceeds the JEFCA critical level of 10 $\mu\text{g/L}$, but is below the permissible levels of the Indian and Bangladesh Governments, i.e., 50 $\mu\text{g/L}$.

Fonseka et al. (2012) present results from a survey of groundwater samples collected from a range of sites, which included CKDu and non-CKDu areas for both water hardness and (As). These are summarized in Table 4.

TABLE 4. Arsenic concentrations in groundwater samples.

Site	Padavi-Sri Pura (n = 36)	Polpithigama (n = 17)	Moneragala (n = 38)	Thanamalwila (n = 19)	Matale (n = 11)	Pasgoda-Deniyaya (n = 10)
	CKDu		Calculus Kidney Disease		Non-CKDu	
Water hardness (mg/L)	270±54 - 820±62	90±8 - 615±47	10±2 - 340±31	170±8 - 500±24	60±5 - 460±21	<60±6
As (µg/L)	21.07±3.54 - 100.91±12.31	2.49±0.61 - 60.55±7.21	2.14±0.84 - 52.47±6.71	1.02±0.08 - 37.1±4.4	39.37±5.21 - 100.42±9.45	0

Source: Fonseka et al. 2012

The authors suggest that there is a strong positive correlation between arsenic content and groundwater hardness. The data does not present the distribution of (As) concentrations nor the means of the samples collected at each site. It is assumed that the data set presented in Table 4 reflects the means and standard error of the mean SE of the triplicate determinations undertaken on each sample. They conclude that the study indicates that (As) associated with elevated levels of hardness can reasonably be one of the potential causes of CKDu. The group has also measured (As) in soils and found maximum levels of 1.5 mg/kg in the vicinity of CDKu areas. These values are lower than the background levels measured in Bangladesh (5 mg/kg) and those on highly contaminated land 10 – 70 mg/kg (Duxbury et al. 2007).

In another study, different water sources have been tested for (As) and cadmium (Cd) (Jayatilake et al. 2013). Ninety nine samples were collected from the drinking-water sources of people with features of CKDu. In three of the samples (As) concentrations were above the WHO standard permissible levels. However, repeated analysis of new samples from the same sources did not exhibit raised (As) values. Further 12 samples collected from Hambantota were also analyzed and were found to be ‘normal’. They conclude that based on these findings drinking-water is unlikely to be ‘the source of (As) and Cd exposure that is causing CKDu’. However, there is a caveat to the above statement. Since there is no central supply of water, and people are using water from a variety of different sources, the findings of these analyses cannot be generalized to assume that (As) and Cd levels in water from all these sources are normal.

In a study conducted by Kawakami et al. (2012) arsenic (As) levels were measured in well water samples collected from Anuradhapura, Nuwara Eliya, Puttalam, Mannar and Jaffna, and the mean concentrations were 0.3, 0.1, 3.7, 7.4 and 1.9 µg/L, respectively. The highest concentrations were observed in samples that were collected from Puttalam, Mannar and Jaffna (range: 8.8–74.0 µg/L), with some samples exceeding the WHO recommendation of 10 µg/L. The authors attributed these high levels to ‘the sandy regosols on the beach and dune sands’, thereby considered them being of geological origin. They also measured the (As) concentrations in rice samples collected from Anuradhapura, and found that none of the samples exceeded concentrations that were found in Japanese rice.

It has been argued in the media that the source of (As) is agro-chemicals that are commonly used by farmers. The Kelaniya University and Rajarata University (As) Group has indicated that their measurements of commonly used pesticides, fertilizers, herbicides, rodenticides and fungicides had high levels of (As), and that was the source of the problem. These findings provoked a significant debate among the scientific community that questioned the methodology used by the proponents. Further analysis by the ROP (Registrar of Pesticides) of samples

collected from a range of distributors found that (As) was present in 2 samples out of 23 samples collected, thereby refuting the claims of the As group. WHO (n. d.) reported that out of 32 samples of agro-chemicals that were analyzed for (As), 10% were contaminated with arsenic and 20% were contaminated with lead. No values, however, were provided in the report.

While water has been seen as a possible source for (As) entering the food chain, Chandrajith et al. (2011a) and colleagues identified relatively high concentrations of (As) in rice samples collected from the CKDu endemic regions, ranging from 100–260 µg/kg. Furthermore, the (As) Group analyzed rice samples from a number of regions, which have been affected by CKDu (Table 5). The high range of (As) concentrations, in general, exceeded those observed in rice samples harvested from contaminated fields in Bangladesh and, the Chinese maximum permissible level of 150 µg/kg for rice. Contrasting these assessment of (As) in rice samples, the ROP with the assistance of the Rice Research and Development Institute (RRDI) of the Department of Agriculture have shown that, in 20 of the samples of rice that were analyzed out of 60 (the results of the remaining 40 were still to be determined) showed no positive levels of the element under investigation.

TABLE 5. Arsenic concentration in rice samples from a range of regions in Sri Lanka.

Region	No. of samples	Arsenic lowest	Arsenic high
(µg/kg)			
Padaviya	16	75.5	897
Sripura	12	67.3	995
Mahawilachchiya	14	33.2	1,074
Mihinthale	10	28.6	808
Kurunegala	12	28.5	656
Monaragala	10	95.0	435
Gampaha	10	36.4	585
Chinese MPL	not known	not known	150

Source: Data adapted from Jayasumana et al. 2013

Finally, Wasana et al. (2012) assessed selected water quality attributes that included F, Al, Cd, As, Ca, Mg (ionic species) and water hardness of samples from high prevalence areas (Padaviya, Kebithigollewa, and Medawachiya Divisional Secretariats [DS] divisions); low prevalence areas (Anuradhapura town area and Pulmoddai area); and from springs (four springs in the Kebithigollewa DS). A selected set of water samples (30 samples from CKDu patients' drinking-water source along with 30 samples from low prevalence areas and springs) were evaluated for (As), and were found to have levels well below the WHO standard of 10 µg/L. The authors conclude that the F, Ca, and Mg levels are much lower in spring water compared to that determined in samples from high and low prevalence areas. Furthermore, the average Cd levels are below the WHO standard of 3 µg/L. Based on these analyses; they conclude that it is advisable to drink spring water in order to reduce the risk of CKDu. However, the authors do not present any evidence supporting the notion that the prevalence of the disease is related to measured water quality attributes.

Review of Articles in the Media Related to Arsenic

A considerable amount of debate and conjecture on the topic of (As), other heavy metals, and agro-chemicals in the etiology of CKDu has been exposed in the media. A brief synopsis of what has appeared in print is presented in Annex 1, to highlight the claims and counter claims of parties who have a vested interest in understanding the causal factors that may contribute to the disease.

Cadmium (Cd) as a Causal Factor

Background

Research undertaken over the last 40 years has identified the irrefutable relationship between the long-term consumption of Cd contaminated rice and the human Cd disease (*itai itai*), which is manifested predominantly by proximal tubular renal dysfunction. This is further confirmed by studies undertaken on dietically exposed populations from non-rice growing areas, which did not identify elevated levels of renal dysfunction in the exposed populations (Baker et al. 1977; Shimada et al. 1977; Ewers et al. 1985; Tohyama et al. 1982; McKenzie-Parnell and Eynon 1987; Strehlow and Barlthrop 1988; Sarasua et al. 1995; Hochi et al. 1995; Osawa et al. 2001; Satarug and Moore 2004; Simmons et al. 2005a). The Cd-induced renal dysfunction in individuals exposed to elevated dietary-Cd is irreversible and progressive, despite decreases in exposure (Nogawa and Kido 1993). In addition, several studies have confirmed that Cd-induced renal dysfunction interferes with vitamin D metabolism, resulting in decreased Ca absorption and the occurrence of osteopenia and osteoporosis, particularly in multiparous women (Kido et al. 1990; Tsuritani et al. 1992).

Research into Cd being a possible causal factor in the development of CKDu in Sri Lanka has been undertaken, and the outcome of this research is discussed below.

Research into Cd

A study undertaken by Bandara et al. (2008) of five reservoirs in the NCP, focused on heavy metal contamination assessed in water, sediment and food samples. They measured significantly higher concentrations of Cd in water samples collected from the five reservoirs. These values ranged from 0.03 – 0.06 mg/L, which were 19-fold higher than the maximum contamination level set by the WHO (0.003 mg/L). The total concentration of Cd in sediment samples collected from the bottom of the five reservoirs ranged from 1.78 – 2.45 mg/kg. The concentrations in sediments did not exceed the European Union (EU) Maximum Permissible (MP) level of 3.0 mg Cd/kg for agricultural (sludge amended) soils (Simmons et al. 2005a).

The mean concentration of Cd in the rhizome of roots of lotus (*Nelumbo nucifera*), a commonly consumed food among rural communities in the affected areas, was found to have extraordinarily high levels of 252.82±12.49 mg/kg (Bandara et al. 2008). They estimated that eating 100 g of the root would amount to consuming 4.53 mg Cd, and that would be equivalent to a 90-fold increase over recommended dietary intake of 0.03 mg/day. The Cd content in rice grains collected from the farms of CRF patients in Medawachchiya, ranged from 0.001 to 0.093 mg/kg in dry weight, with a mean value 0.0444 mg/kg±0.0165. The Cd content in rice grain in the Anuradhapura–Thuruwila area was 0.001–0.194 mg/kg, with a mean value of 0.0404 ± 0.0196. They concluded that all samples collected tested positive for Cd content, and that the background value for rice grain Cd in Sri Lanka was found to be 0.001 mg/kg. The maximum permissible level of Cd in rice grain

according to Codex Alimentarius Commission (2002) is 0.2 mg/kg. In a study of rice grain Cd concentrations from samples collected from 1,067 fields in western Thailand where contamination of soils had taken place, the concentration ranged from <0.01 – 7.75 mg Cd/kg (Simmons et al. 2005b). These values were up to 38.75 times the recommended ML value for Cd in Thai rice grain of 0.2 mg Cd/kg. Furthermore, over 83.0% of the fields sampled produced rice grain with Cd concentrations exceeding the recommended ML for Cd in Thai rice grain. Clearly, the samples collected in the Bandara et al. (2008) study were below permissible international levels, however, the authors concluded that continued exposure to these levels of Cd in rice would have an adverse effect on the kidneys in the long run.

The Cd content in muscles of the freshwater fish *Oreochromis niloticus* collected from two of the reservoirs, namely Karapikkada and Thuruwila in the North Central Province (NCP) showed a mean and maximum Cd concentration of 0.0575 and 0.1150 mg/kg (Karapikkada), and 0.2022 and 0.4250 mg/kg (Thuruwila), respectively (Bandara et al. 2008). While their data does not present a frequency distribution of Cd concentrations, they have used the maximum measured concentrations in each of reservoirs, to estimate maximum weekly intake of Cd from a combination of rice and fish. They conclude that the average weekly intake of Cd by residents in a region, whose diet is rice and fish, which are produced from waters sourced from these reservoirs that carry heavy levels of Cd in the sediments, is higher than the maximum contaminant level of 7 µg/kg body weight. Therefore, further strengthening their hypothesis of Cd being the causal factor in CRF observed in the region.

The aforementioned research also measured the amount of Cd excreted in the urine (UCd) of CRF patients, and found that the levels were significantly different to that of asymptomatic residents in the same area. The UCd levels, in both CRF patients and asymptomatic individuals, were higher than the recommended 5.00 µg Cd/g creatinine. The WHO standards stipulate that a urinary excretion of 2 µg Cd/g creatinine is normal, while 10 µg Cd/g creatinine is indicative of an irreversible situation of chronic exposure and potential renal dysfunction (WHO 2000). In the study of Bandara et al. (2008), the subjects tested had UCd levels above 5 µg Cd/g creatinine, and went as high as 13.92 µg Cd/g creatinine. In a study undertaken by Chandrajith et al. (2011a), they compared the results of UCd measured on patients and asymptomatic individuals from the Giradurukotte and Medawchchiya regions of the NCP, and recorded values ranging from 0.390 – 0.788 µg Cd/g creatinine, which are significantly lower than those observed by Bandara et al. (2008).

Athuraliya et al. (2003), working in the NCP, reported that the CRF patients exhibited tubular interstitial type renal disease, which is an indication of involvement of Cd. Renal biopsy reports of CRF patients at Medawachchiya in 2007 revealed that endocytosis and proximal tubular sclerosis were predominant; and that no glomerular renal dysfunction was observed, suggesting a possible involvement of chronic exposure to Cd (Bandara et al. 2008).

The source of Cd contamination is posited by the authors to be through the use of agro-chemicals and, in particular, triple super phosphate (TSP), where there has been a significant increase in the importations of this fertilizer since 1974 (Bandara et al. 2008). Measurements made on the Cd concentration of TSP are presented as 71.739 mg Cd/kg P₂O₅, and based on the imports since 1973, a total of 68.9 tonnes of Cd has been added to agricultural land in Sri Lanka by 1984. They argue that due to the prevalence of high rainfall in the upland regions, Cd is leached into waterways that eventually end up in reservoirs of the Mahaweli River Diversion Scheme, which is then used to irrigate rice crops as well as aquatic species. Additionally, Cd pollution through the use of the herbicide 'bispyribac sodium', commonly used by farmers, has been found to contain 0.5 mg Cd/L (Bandara et al. 2008).

Bandara et al. (2008) also note that in a food habit survey undertaken among farmer families, the traditional 'priority serving of food' is practiced. As such, females in the house (mother and the daughters) are usually served only with the gravy of a fish curry while the fish portions are served very rarely, i.e., if there is any leftover after the males have been served. Females tend to consume a lesser quantity of rice. They suggest that due to this differentiation in food intake one could assume that there would be a higher provisional tolerable weekly intake (PTWI) among male farmers.

It is pertinent to compare the measured Cd levels in water and food samples from a range of studies undertaken in Sri Lanka. Bandara and colleagues have been published widely in this respect in peer reviewed articles. The rice Cd concentrations from a range of publications are presented in Table 6. It is clearly evident, that there is a range of Cd concentrations that have been measured predominantly in rice samples collected from the households of patients that have been diagnosed with CRF within areas of Sri Lanka, where the disease is prevalent. In all cases the concentrations that have been measured fall below the modified Codex Alimentarius Commission (2009) recommendation for rice of 400 μg Cd/kg. Furthermore, the measured values in rice grain were significantly lower than those measured by Simmons et al. (2003) from samples collected from rice paddy systems, where Cd contamination had occurred and linked to CRF. It is of note, that the range of concentrations of Cd determined in the study of Bandara et al. (2010a) was substantially lower than those reported previously. It is not clear what contributing factors would account for these differences, as both sets of samples were collected from households of patients suffering from CRF and within the same general geographical area. This same argument would apply to the large differences in Cd concentrations in lotus, fish samples and milk in the two manuscripts of Bandara et al. (2008, 2010a), which leads one to question the validity of these figures and, therefore, warrants further systematic studies. Furthermore, Chandrajith et al. (2011a) measured the Cd concentrations in rice samples collected from the households of CKDu patients, and recorded substantially lower concentrations than Bandara et al. (2008, 2010a) (Table 6).

Bandara et al. (2008, 2010a) along with others argue that long-term exposure to food with elevated Cd levels can result in the development of CRF, and question the validity of the current safe levels recommended by Codex with the existing high tendency of environmental exposure. The same argument could be universally applied, yet we do not see similar levels of CRF globally. Hence, the current justification by Codex would stand.

The source of Cd has been argued to be associated with the increased use of agro-chemicals, namely, TSP and selected herbicides that have contaminated soils and water bodies (Bandara et al. 2008, 2010a). A comparison of soil and sediment extracted values from sources assumed to be contaminated by Cd in Sri Lanka are presented in Table 7, and are compared to those of Simmons et al. (2003). While the extraction methodologies differed between Bandara and Simmons, the values reported by the latter for paddies known to be contaminated are in accordance of magnitudes larger than those of Bandara (Table 7). Furthermore, the samples analyzed from cultivated soils in the study of Bandara et al. (2008) are in accordance of magnitudes higher than those reported in the study reported in 2010 (Bandara et al. 2010a) (Table 7). The situation becomes even more confused when Bandara et al. (2010b) report exchangeable Cd levels to range between 0.32 and 1.24 mg Cd/kg of soil, these values in most cases exceed the total Cd values (Table 7).

Water sources have been implicated in the distribution of Cd as well as a source by which Cd enters the food systems, both directly (drinking water) and indirectly (accumulation in food crops). Bandara et al. (2008) analyzed water samples from five main reservoirs for dissolved heavy metals. These reservoirs had communities in which over 5.6% of farmers exhibited elevated levels proteinuric, evidence of CRF. They reported elevated levels of Cd, all of which were in accordance of magnitudes

TABLE 6. Selected levels of Cd concentration in food sources commonly consumed by rural communities in the NCP of Sri Lanka. All data converted to common units.

Food Source	Units	Values	Reference
<i>Rice</i>			
Medawachchiya – CRF patients households	µg/kg	Mean = 44.4 Range = 1–93	Bandara et al. 2008
Anuradhapura – Thuruwila area – CRF patients households	µg/kg	Mean = 40.4 Range = 1–194	Bandara et al. 2008
Random selected patients households	µg/kg	Mean = 23.4 Range = 1.7–92.5	Bandara et al. 2010a
Giradurukotte area - CKDu patients households	µg/kg	Range = 9–18	Chandrajith et al. 2011a
Nikawewa area - CKDu patients households	µg/kg	Range = 3–13	Chandrajith et al. 2011a
Thai Rice study	µg/kg	Mean = 1,830 Range = 20–5,000	Simmons et al. 2003
Codex Committee	µg/kg	400	Codex Alimentarius Commission 2009
<i>Pulses</i>			
<i>Vigna radiata</i>	µg/kg	Mean = 31.8 Range = 2.1– 99.2	Bandara et al. 2010a
<i>Fish</i>			
Tilapia (<i>Oreochromis niloticus</i>)	µg/kg	Karapikkada: Mean = 57.5 Maximum = 115.0 Thuruwila: Mean = 202.2 Maximum = 425.0	Bandara et al. 2008
Tilapia (<i>Oreochromis niloticus</i>)	µg/kg	Mean = 21.8 Range = 0.5 – 90.7	Bandara et al. 2010a
<i>Lotus</i>			
<i>Nelumbo nucifera rhizomes</i>	µg/kg	Mean (n = 14): 252,820	Bandara et al. 2008
<i>N. nucifera</i>	µg/kg	Mean = 46.4 Range = 2.3–271.3	Bandara et al. 2010a
<i>Milk</i>			
Cow milk samples	µg/L	Mean = 100 Range = 50–150	Bandara et al. 2008
Cow milk	µg/L	Mean = 14.01 Range = 0.1–84.3	Bandara et al. 2010a

higher than the maximum concentration levels for drinking water as set out by the WHO (Table 8). This initial study was followed up by a comprehensive assessment of water samples collected from 21 tributaries, which contributed to the Mahaweli Diversion Scheme (Bandara et al. 2010b). The study reported that in all of the catchment areas the tributaries had Cd levels that ranged from 3.9 to 23 µg/L, all exceeding the WHO contamination level (Table 8). They found that the minimum level of

Cd contamination occurred in the predominantly tea growing areas of the watershed, and attributed this in part to the low input of Cd from the type of phosphate fertilizer used in the tea plantations. Tea estates predominantly use unprocessed rock phosphate, namely, Eppawala rock phosphate (ERP) at relatively low rates. The source of this rock phosphate is local, coming from Eppawala, Anuradhapura, Sri Lanka, and it contains low levels of Cd (Bandara et al. 2010b) (see discussion below on sources of contamination). In a subsequent study of the five reservoirs sampled by Bandara et al. (2008) and Chandrajith et al. 2011a revisited the same sites and undertook a survey of waters in the reservoirs. The concentrations of Cd measured were in accordance of magnitudes lower than those measured previously (Table 8), thus questioning the validity of the conclusions of Bandara et al. (2008). Based on the values presented in both Tables 7 and 8 associated with studies undertaken by Bandara and colleagues, it is suggested that there may have been issues associated with the analytical methodology.

Sources of the contaminant have been attributed to increasing use of agro-chemicals and, in particular, to TSP (Bandara et al. 2008, 2010a, 2010b). They report concentrations between 23–71 mg Cd/kg of TSP (Bandara et al. 2010b). Nevertheless, Dissanayake and Chandrajith (2009) reported a range of concentration (2.3–46.1 mg Cd/kg of TSP) based on a survey of TSP fertilizers retailed in the NCP. It is well recognized that phosphatic fertilizers and, in particular, TSP, do carry a range of heavy metal pollutants that are a reflection of the inherent impurities within the source material. Furthermore, if one considers that TSP is used throughout Sri Lanka as a P source in agricultural production systems and that it is the predominant source of Cd, one would intuitively expect to find CRF within in all agricultural ecotypes where it is used. However, this does not seem to be the case. Chandrajith et al. (2011a) conclude that although early studies attributed the etiology of CKDu to the elevated concentration of Cd (Bandara et al. 2008), the results could not be replicated in their study, and no such high Cd levels were observed in drinking-water, surface water, rice and urine samples. Therefore, the involvement of Cd on the CKDu can be eliminated. They conclude by suggesting that it is very likely, the unique hydrogeochemistry of the drinking-water is closely associated with the incidence of the disease (Chandrajith et al. 2011a).

TABLE 7. Concentration of Cd in soil and sediments as reported in selected literature.

Source	Units	Values	Reference
<i>Sediment (reservoir names)</i>			
Kunbichchankulama	mg/kg	Mean = 2.42	Bandara et al. 2008
Alankulama	mg/kg	Mean = 2.45	Bandara et al. 2008
Thuruwila	mg/kg	Mean = 2.18	Bandara et al. 2008
Karapikkada	mg/kg	Mean = 1.78	Bandara et al. 2008
Ullukkulama	mg/kg	Mean = 1.87	Bandara et al. 2008
<i>Soil samples</i>			
Perimeter soils of reservoirs ¹	mg/kg	Range = 0.56–1.050	Bandara et al. 2008
Uncultivated soils ¹	mg/kg	Range = 0.0052–0.230	Bandara et al. 2010a
Cultivated and TSP applied ¹	mg/kg	Range = 0.0159–0.1104	Bandara et al. 2010a
Exchangeable Cd in up-country soils	mg/kg	Range = 0.32–1.24	Bandara et al. 2010b
Thai paddy systems ²	mg/kg	Range = 3,900–284,000	Simmons et al. 2003
Thai paddy systems ³	mg/kg	Range = 2,250–22,000	Simmons et al. 2003

Note: ¹ Acid digest with HNO₃ and HCl; ² Acid digest Aqua Regia-digested; ³ 0.005 M DTPA-Extractable

TABLE 8. Cadmium (Cd) levels measured in water samples from a range of studies in Sri Lanka.

Source	Units	Values	Reference
<i>Reservoir name</i>			
Kunbichchankulama	µg/L	Mean = 50 ¹	Bandara et al. 2008
		Mean = 0.0037	Chandrajith et al. 2011a
Alankulama	µg/L	Mean = 40 ¹	Bandara et al. 2008
		Mean = 0.0029	Chandrajith et al. 2011a
Thuruwila	µg/L	Mean = 60 ¹	Bandara et al. 2008
		Mean = 0.0029	Chandrajith et al. 2011a
Karapikkada	µg/L	Mean = 60 ¹	Bandara et al. 2008
		Mean = 0.0081	Chandrajith et al. 2011a
Ullukkulama	µg/L	Mean = 30 ¹	Bandara et al. 2008
		Mean = 0.0033	Chandrajith et al. 2011a
21 tributary rivers of the Mahaweli Scheme	µg/L	Range = 3.9–23	Bandara et al. 2010b
WHO maximum contamination level for drinking water	µg/L	3.0	

Note: ¹Values represent the mean of 30 samples

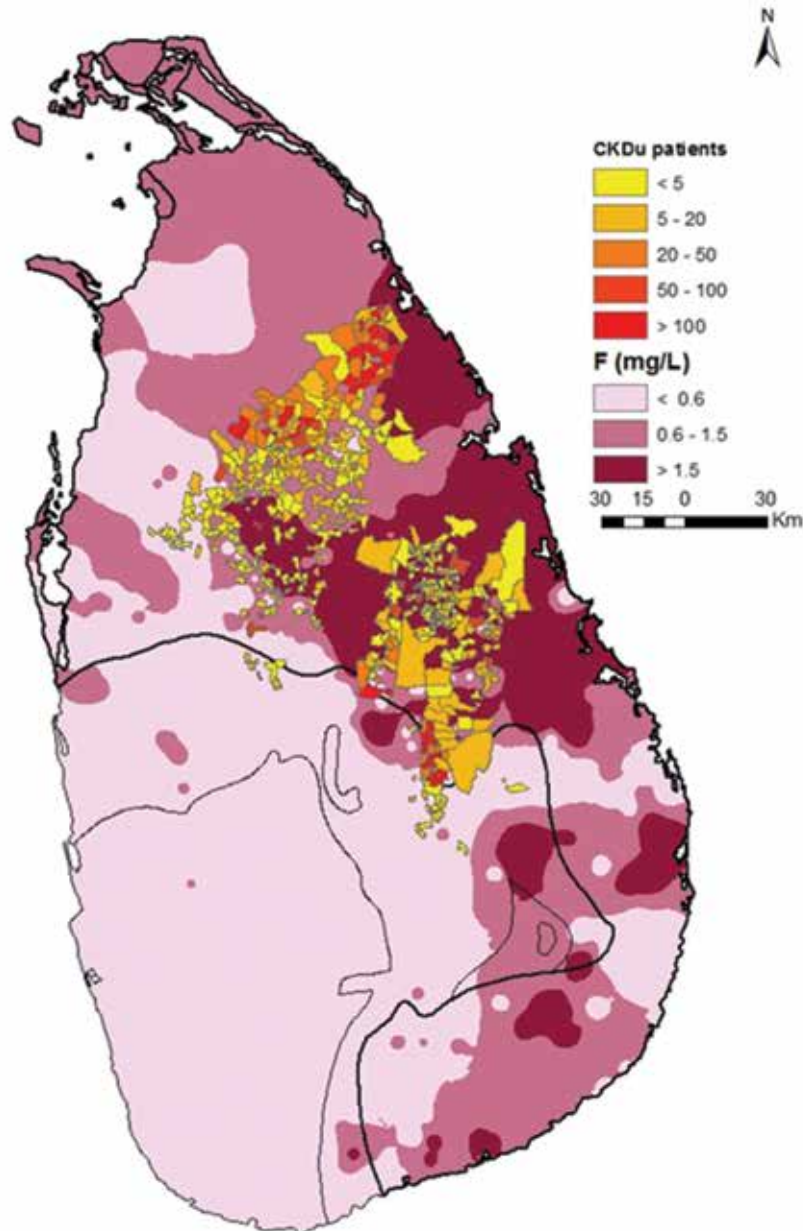
The involvement of Cd as a causal factor is revisited in the work of Jayatilake et al. 2013. It re-confirms the suggestion that chronic exposure of people in the endemic area to low levels of cadmium is through the food chain, and considers it a risk factor for the pathogenesis of CKDu. Furthermore, the study suggests that, deficiency of selenium and genetic susceptibility among persons with CKDu may be predisposing factors for the development of CKDu.

Fluoride and Aluminum

The etiology of CKDu has been the subject of numerous studies over the last decade, in which most research has focused on the geo-environmental factors due to its unique geographic distribution. An observation that can be gleaned from the spatial prevalence of the disease is that it overlaps regions in the country that are known to have high groundwater fluoride (F) levels. Dissanayake (1996) suggested that there was a possible link between the fluoride content of drinking-water and the prevalence of the CKDu; this in part is supported by overlaying the incidence of the disease with F water quality data (Figure 4). It should be noted that values of F concentration exceeding 1.5 mg F/L were used to create the map, although as will be seen in the discussion below, that concentrations lower than this value have been implicated in the development of the disease.

There has been a resurgence of interest in the quality of drinking-water in relation to CKDu, since shallow- and deep-wells are the predominant source of potable water in affected regions. For example, nearly 87% of the population in the Anuradhapura administrative district in the north central region, where most areas are affected by CKDu, use either dug well or tubewell water (Perera et al. 2008). Water is withdrawn directly from the wells and consumed without any treatment, except boiling in most cases (Chandrajith et al. 2011a).

FIGURE 4. Map describing the prevalence of CKDu and groundwater fluoride concentrations.



Source: Created by the authors in 2013

Among the studied regions that Chandrajith et al. (2011a) assessed in their water quality study, the Giradurukotte area exhibited a mean F content of 0.63 mg/L, where the maximum F level recorded was 2.14 mg/L. The Nikawewa area also shows higher fluoride content in the groundwater, with a mean value of 1.41 mg/L and with a maximum of 4.80 mg/L. Fluoride levels in the Medawachchiya area, which is one of the hotspots for CKDu, vary from 0.52 to 4.90 mg/L with an average of 1.02 mg/L. The non-endemic region of Huruluwewa in the north central dry zone also contained higher fluoride with an average of 1.03 mg/L. The mean values of fluoride are not significantly different ($p > 0.005$) among the three studied regions. However, in all studied regions, dental and skeletal fluorosis is widespread. Clearly, there seems to be no obvious distinction between in F concentrations in drinking-water sources between endemic and non-endemic areas.

A further evaluation of the data collected in the aforementioned study is presented in Chandrajith et al. (2011b). In their re-analysis of the water quality attributes from the four endemic sites and two non-endemic sites, they show differences in Na^+ and Ca^{2+} activities⁴ in drinking-water between affected and non-affected regions, as evidenced by their Na/Ca ratios. Although high fluoride levels were common to all studied regions, non-endemic areas were characterized by higher Na/Ca ratios. They put forward the notion that with an increased Na/Ca ratio, the geochemical behavior of drinking-water is favorable for the complexation of fluoride with Na^+ , which reduces both the toxicity of fluoride ions in the human body and the absorption of Ca^{2+} . Conversely, higher Ca^{2+} activity aggravates the damage caused by fluoride, resulting in possible lesions on tubular cells leading to their death. They further suggested that, the nutritional status of individuals and genetic predisposition also play a major role in CKDu, where only susceptible members of the family or families are affected, although all of them are exposed to similar geo-environmental conditions. Farming communities in such regions, who mostly depend on their immediate natural environment, become more vulnerable to the disease as they drink more water (obtained from the ground) when working under warm humid conditions that prevail in the dry zone of Sri Lanka. They concluded, based on this assessment that groundwater used for drinking and domestic purposes may have unique fluoride, sodium and calcium ion concentrations, which could lead to fatal chronic kidney diseases (Chandrajith et al. 2011a). This is a plausible explanation, for the prevalence of the disease within a geographical mosaic that is re-enforced through a genetic predisposition of an individual. However, they do not present data to support the genetic predisposition of households that draw water from the sources that were sampled. Furthermore, it is only assumed that this data may have been collected. In addition, results from chemical speciation of the water samples were not presented, which would suggest that this assessment was not undertaken. However, the question remains why then has the prevalence of CKDu appeared to increase since the 1990s?

In most cases, the F content in well water in these regions does not exceed the WHO recommended limit of 1.5 mg/L, in general, but in most samples the F contents were above the 0.5 mg/L, the limit recommended for tropical countries by WHO, in particular (WHO 1994). Warnakulasuriya et al. (1992) have argued that the WHO recommended levels of 1.5 mg/L F in drinking water should not be applicable for hot and dry climates as prevalent in the dry zone of Sri Lanka, since people consume higher volumes of water on a daily basis to regulate the water balance and, thus are predisposed to higher levels of F.

Illeperuma et al. (2009) attributed the prevalence of CKDu in the NCP to the use of poor-quality aluminum (Al) utensils for cooking purposes and storing of drinking water, which increases the rate of dissolution of Al, if the water contains high levels of fluoride. In studies undertaken to assess the leaching of Al from these utensils, they found that in the absence of F the concentration of Al was 0.43 mg Al/L. However, in the presence of 1.0 mg F/L the dissolution rate increased to 11.9 mg Al/L., and under acidic conditions obtained during the use of tamarind at a pH of 3.02, the Al leached was around 18 mg Al/L even in the absence of fluoride with a regular enhancement of leaching at higher fluoride levels. Aluminum leached at 6 mg/L fluoride reached 29 mg/L after 10 min of boiling. Similarly, at a pH of 2.12 in the presence of 0.1 M tartaric acid, the maximum aluminum concentration leached reached approximately 50 mg/L. They put forward the notion that alumino-fluoride complexes may play a significant role in causing chronic renal failure. However, Chandrajith et al. (2011a) question the validity of this argument based on the fact, that they do not put forward a plausible reason for the lack of the existence of the disease in non-endemic regions with extremely high drinking-water fluoride found within the dry zone region, e.g., Ampara, Monaragala and Hambantota among others where similar kinds of utensils are used.

⁴The authors use the term 'activity' on an ionic species without presenting any evidence that a solution speciation model had been used to calculate the individual ionic activities of all species that make up the water samples. We have sort clarification from the authors on this matter.

WHERE ARE THE GAPS THAT IWMI COULD ASSIST IN FILLING?

- The question as to why NCP might be a focal area is not fully understood. The environmental factors suggested are present in other parts of Sri Lanka as well. Therefore, it clearly demonstrates the need for more detailed investigations in the hotspots where there is a high prevalence of the disease. The emerging evidence, though inconclusive, suggests an interplay of multiple agents, including environmental factors and genetic predisposition that make some groups of people more vulnerable than others. We propose water as an entry point to look at this unresolved problem, and suggest hydrogeological studies coupled with patient behavioral aspects to understand some of contaminant pathways that might have been altered in the last 10-15 years, the time period during which the first cases were reported.
- Is there a pattern of disease prevalence linked to the ancient irrigation systems? Or over abstraction of groundwater through the agro-well systems in the hotspots leading to geochemical imbalances? How does it enter the food chain?
- Confirmation of the possible role of F in the development of the disease. The activity of specific ionic species (Ca, Na and Mg) in the solution would appear to have not been assessed in the literature that has been reviewed. There is an opportunity to assess this aspect based on data sets that have been collected through the application of chemical speciation models.
- Re-visit the patient classification and study the distribution of the disease among age classes, as there have been several independent studies undertaken with no attempt to consolidate the databases collected on patients and disease into a single repository.
- Taking 2002 as the point at which clinicians became concerned over the incidence of the disease, it would be interesting to go back further in time to see whether there was a point where the incidence of the disease in the NCP was at the same level as that of the other provinces.

A possible role for IWMI could be to partner with key stakeholders in developing a comprehensive initiative on assessing water attributes of groundwater that would focus on both agro-wells and deep wells, in affected and non-affected areas.

In assessing progress to understand the causal factor(s) associated with the development of the disease, a general observation of the research effort to date is that it has been opportunistic, uncoordinated at times and in certain cases contradictory. It is anticipated that the long awaited report of the WHO and Ministry of Health will in part address some of the contentious aspects and shed some light on the causal factor(s) that are contributing to the development of the disease.

The issue of CKDu has significant ramifications for the Government of Sri Lanka and the country's health system. Without an understanding of the causal factors contributing to the development of the disease, medical services will undoubtedly be placed under considerable pressure, along with households that are affected by the disease. Clearly, these services cannot cope with the current situation, and in the majority of cases the diagnosis of CKDu is, in effect, a death sentence with associated social consequences.

DISCUSSION

In assessing progress to understand the causal factor(s) associated with the development of the disease, a general observation of the research effort to date is that, it has been opportunistic, uncoordinated and in certain cases contradictory. A more systematic approach appears to have been followed in the most recent study (Jayatilake et al. 2013).

What Conclusions can be Drawn from the Research to Date?

- A higher prevalence of CKDu is reported among male farmers, over 40 years of age, living in the NCP. The ratio of male to females affected by the disease is reported to be between 3:1 and 2.4:1. The patients are predominantly subsistence farmers and / or agricultural laborers. There is also anecdotal evidence to suggest that the age of patients diagnosed with the disease is declining, propounding that the disease is being reported among younger cohorts of the population. There is a need to study the distribution of the disease among age classes, as there have been several independent studies undertaken with no attempt to consolidate databases collected on patients and disease into a single repository. However, the recent WHO publication suggests that more females are affected than men, which is a new finding.
- To date CKDu has been reported from the Central Province (CP); Eastern Province (EP); North Central Province (NCP); Northern Province (NP); North West Province (NWP); Southern Province (SP); Sabaragamuwa Province (SABP); Uva Province (UP); and the Western Province (WP). Observing the overall CKD, in the North Central Province (NCP) it is 3-4 times higher than that of most provinces, other than the NP. As early as 2002, three times the national average of CKD patients were found in the NCP. It is not clear whether the progressive increase in patients being diagnosed with CKD with time, is due to increased awareness of the disease, improved diagnostic techniques or to an increase in patients presenting with signs of CKD. Taking 2002 as the point at which clinicians became concerned over the incidence of the disease, it would be interesting to go back further in time to see, whether there was a point where the incidence of the disease in the NCP was at the same level as that of the other provinces. In addition, the NCP serves as a focal area in which the prevalence of the disease is higher than other provinces, why begs the question in relation to this situation, and may also suggest an environmental and / or genetic predisposition.
- CKDu is not confined to Sri Lanka, but occurs elsewhere globally, e.g., India and Central America. A hypothesis that has been put forward as to why farmer cohorts are predisposed to the disease, is that they undertake strenuous labor under hot climatic conditions that may lead to chronic dehydration and greater consumption of water. They, more often than not, appear to consume home grown alcoholic brews. This would suggest that water and its constituents may in part play a role in the etiology of the disease, a view that is held by several parties in Sri Lanka who we have contacted.
- A gamut of causal factors that are of environmental nature has been suggested. Among these are As, Cd, F and Al. A few others, such as snake bites, Ayurvedic medicines, consumption of alcohol and aflatoxins also have been suggested.
 - i. While a considerable amount of media attention has been leveled at (As) as a significant factor in the disease, all of the material reviewed on this assumption

has been in non-peer reviewed publications, thus making it difficult to verify the veracity of these assertions. There are conflicting opinions among clinicians over patients manifesting recognized symptoms that are common to communities afflicted with arsenosis.

While elevated levels of (As) are reported to have been measured in groundwater samples collected by groups working on the issue, the strongest endorsement that (As) is not viewed as a candidate for the development of the disease comes from the WHO. In their study of groundwater samples collected from areas identified as hotspots for CKDu, (As) levels were found to be 'normal'. Furthermore, there have been reports that (As) was entering the food chain through the consumption of rice, however, analysis of rice samples collected from households of patients affected by the disease did not indicate overtly high levels of As, and were well below the levels set in China.

- ii. Cadmium (Cd) has been implicated as a causal factor contributing to the disease, the source of contamination being triple super phosphate (TSP). Elevated levels were reported in waters from reservoirs within the Mahaweli Diversion Scheme, soils, and in a range of foods commonly consumed by rural communities. Levels measured in soils and rice samples by one of the groups appeared to be elevated, but they were not as high as those measured in Thailand where known Cd-related kidney disease had been identified. Further studies have questioned the veracity of these results. It is difficult to reconcile the role of Cd in the disease, as TSP is used ubiquitously throughout the agricultural sector in Sri Lanka and elsewhere. One would, therefore, expect to find the incidence of the disease throughout Sri Lanka, which is not the case. Hence, it is unlikely that Cd plays a significant role in the development of the disease.
 - iii. What does appear as a potential causal factor in the development of the disease is fluoride in the groundwater and, its interaction with other constituents that are present, namely, Ca, Na and possibly Mg. There is evidence to suggest that the disease is confined to areas where high levels of F are present in the groundwater, and that is not the concentration of F per se, but rather the interaction of F with constituent ions in the solution. This has still to be confirmed. However, this could be an area in which IWMI could conduct research. The activity of specific ionic species in the solution would appear to have not been assessed. There is an opportunity to assess this aspect based on data sets that have been collected through the use of chemical speciation models.
 - iv. It is also suggested that Al vessels may have a role to play in the development of the disease, but, the supporting evidence has to be investigated further, with reactive species modeling.
 - v. There is very little supporting evidence to infer aflatoxin contamination as a significant causal factor responsible for the development of the disease in Sri Lanka.
- While all of the above possible causal factors would not explain the somewhat random but focal presentation of the disease in affected areas, there is a growing body of knowledge that would suggest a genetic link to the problem that predisposes certain individuals to the

disease. We are aware that a peer-reviewed article is currently being prepared that supports this hypothesis.

- The disease appears to be familial, as seen in a few studies. A genetic link to the disease is being investigated.

The issue of CKDu has significant ramifications for the Government of Sri Lanka and its health providers. Without understanding the causal factors contributing to the development of the disease and addressing them, medical services will undoubtedly be placed under considerable pressure along with households affected by the disease. Clearly, these services cannot cope with the current situation, and in the majority of cases, the diagnosis of CKDu is in effect a death sentence with associated social consequences.

There is evidence to suggest that water quality is a contributory factor in the development of the disease. For the villages that are adversely affected, the government is providing safe drinking-water. The impact of providing safe drinking-water has to be further evaluated.

IWMI has the capability to contribute to this effort. With its hydrogeological and spatial modeling capabilities, a possible role for IWMI could be to partner with key stakeholders in developing a comprehensive initiative on assessing water attributes of groundwater, which would focus on both agro-wells and deep wells in affected and non-affected areas. As there is a clear link between the disease and the source of water, (i.e., it would appear that all affected communities are sourcing their water from either shallow or deep wells) it may be valuable to investigate further, the entire water cycle, from a aquifer point of view, to understand the geogenic as well as other contaminants that may be contributing to this debilitating disease.

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ANNEX 1

A report in the Daily News dated June 30, 2012, indicated that research undertaken by the Health Ministry with the technical support of the World Health Organization (WHO) had revealed that one of the key causative factors for CKDu affecting people in the North Central Province is co-exposure to low concentration of nephrotoxic heavy metals. These nephrotoxic heavy metals include cadmium (Cd) and arsenic (AS). The research has revealed that heavy metals enter the body mainly through the food chain and possibly through air pollution. It also revealed that water is not the source of this exposure. However, according to the study, improving water quality and lowering the current levels of heavy metals in soil can help to reduce the body burden of heavy metals. It also stated that, prevention of indiscriminate use of fertilizer and certain pesticides that harm kidney properties, can help to protect the vulnerable segments of the population.

The Island, August 15, 2012

Head of the Chemistry Department, University of Kelaniya, Prof. Priyani Paranagama, said that 95% of patients had used hard water with high levels of heavy metals and poisonous arsenic. The research had revealed the presence of arsenic in CKD patients. Over 80% of the patients had arsenic in hair, nails and urine.

http://www.island.lk/index.php?page_cat=article-details&page=article-details&code_title=59316

The Island, March 16, 2011

Dr. Channa Jayasumana of the Department of Pharmacology of the Faculty of Medicine, Rajarata University, said that certain types of soil, such as those with high calcium content, have more arsenic retention ability; and that previous research has shown our dry zone rice-field-soils are characterized by a high content of calcium compared to those of the wet zone. Previous research had also identified comparatively high amounts of arsenic in rice collected from CKDu endemic regions, such as Giradurukotte and Nikawewa, but had not correlated the findings with the prevalence of kidney disease. However, our analyses have revealed high amounts of arsenic in rice, that is, 100-500 ug/kg, which are compatible with the arsenic content in rice in West Bengal and Bangladesh. Besides, in our investigations of the hair samples of CKDu patients, a high arsenic content of 3.04-7.18 mg/kg was observed. Arsenic forms strong bonds with calcium and is difficult to elicit in 'hard water'. The areas worst hit by CKDu were, Girandurukotte 2,500 patients, Medawachchiya 2,000, Padaviya 1,400 and Medirigiriya 600. In some of these areas, hyper-pigmentation and keratosis in the palms and soles of patients were observed.

http://www.island.lk/index.php?page_cat=article-details&page=article-details&code_title=20846

The Island, June 8, 2011

Prof. Nalin de Silva said that the arsenate compounds responsible for the Rajarata Chronic Kidney Disease Unidentified Etiology (RCKD un et) are formed only when arsenic is mixed with hard water found in the Rajarata areas. As arsenic is not found naturally in Sri Lankan soil, we wanted to find out how arsenic got into the soil and the water in Rajarata. The suspect was nearer at hand and, it was nothing other than the agro-chemicals.

Sunday Observer – Arsenic (dated June 12, 2011)

The research team proved the agro-chemicals contained arsenic in alarming proportions in the pesticides. The 'hard water' (called kivil in the local language) present in the area helped the arsenic to form calcium arsenate $\text{Ca}_3(\text{AsO}_4)_2$, an extremely poisonous chemical compound that is water soluble.

Prof. Nalin de Silva said that they were 100% certain, that there are alarming proportions of arsenic content in the agro-chemicals imported to Sri Lanka. But we need more tests to confirm that this is the cause for CKDu observed in Rajarata.

Head of Chemistry Department, Prof. Priyani Paranagama, said that the tests on agro-chemicals proved that their products contained arsenic levels ranging from 100 to 3,000 micro grams per kilogram, which is a highly lethal proportion capable of causing arsenic poisoning among humans. "We found higher proportions of arsenic content in the body parts; it was over 10-15% higher than the WHO recommended levels." Dr. Chinthaka Wijewardena of Padavi Sripura Hospital (who tested the dead bodies assisted by a Judicial Medical Officer) said a shocking 500 people out of the tiny 10,000 population in Padavi Sripura have been diagnosed with this killer disease. He has learnt 40% of deaths in this area during the past 5 years were caused by the CKDu.

The Nation - Arsenic (dated, June 19, 2011)

Prof. Padmini Paranagama, Head of the Chemistry Department at Kelaniya University and her team tested around 50 commonly available agricultural chemicals, and over half of them were found to contain arsenic in the range of 1,000-3,000 parts-per-billion (ppb). "We found arsenic not only in rice grown in the area, but in vegetables, cucumbers, corn, and even in the margosa (called *kohomba* in the local language) trees in the area as well. It's everywhere," said Dr. Channa Jayasumana who was part of the research team. According to the Rice Research and Development Institute (RRDI), there is no set maximum permissible level of arsenic that has been set for rice in Sri Lanka, but the figure that China regulates is 150 ppb. RRDI says they tested 60 samples of rice, and have obtained the results of 20 of them.

The Sunday Leader, June 19, 2011

By Dr. Anura Wijesekara – Registrar of Pesticides

The story unfolded in the media on arsenic (As) not being traced in rice and pesticides, has given the impression that arsenic is not present in the unspoiled environment of Sri Lanka. This is fiction. Arsenic is the twentieth most abundant element in the world, and there is ample scientific evidence to show (As) is also present in Sri Lanka's environment, including soil, water, living organisms and even in the human body, albeit in very minute quantities. Of course, chronic (As) poisoning can occur if considerably high amounts of (As) are accumulated in the body. Most of the measurements on arsenic are total (As). It is also important to understand that only the inorganic (As) can accumulate and be poisonous. Organic (As) is usually excreted by the human body.

It is important to be informed that not only rice but many food items, including wheat flour contain minute amounts of (As) in them. Usually seafood has relatively higher amounts of (As). The Gazette Notification of June 6, 2001 has prohibited, among others, the importation of pesticides with (As) or mercury as their active ingredient. It does not provide any authority to prohibit importation of pesticides with (As) or mercury as minute impurities. However, the ROP office guarantees that no pesticide with high levels of (As) or mercury has been registered in Sri Lanka.

Link: <http://www.thesundayleader.lk/2011/06/19/arsenic-upheaval-the-truth-and-fiction/>

Sri Lanka Guardian, June 15, 2011

By Nalin de Silva

According to the tests, which are supposed to have been carried out at the ITI, arsenic is present in two brands of pesticides out of about ten. The Group at Kelaniya is happy and feels vindicated that at least two brands of pesticides have been tested positive for arsenic (As). If not for the experiments carried out at the University of Kelaniya, nobody would have suspected of arsenic being in pesticides, and the particular brands of pesticides would have been still available in the market. It was the group at Group at Kelaniya that investigated into the prevalence of the chronic kidney disease (CKD) in Rajarata, who first came out with the fact that arsenic is present, at least, in the samples of pesticides and the samples of water that was collected by them from Rajarata areas.

Link: <http://www.srilankaguardian.org/2011/06/devivaru-arsenic-and-science.html>

Daily FT, June 14, 2011

By Shezna Shums

In order to test the validity of such a concern (rice contaminated with arsenic), the Ministry of Agriculture of Sri Lanka did a testing in the Industrial Technology Institute's laboratory using 28 samples of suspected pesticides and 60 samples of paddy from the respective area. The test proved that while only 2 of those 28 pesticide samples contained arsenic and that too at a minute level, none of the paddy samples tested positive. Thus, it leads to the conclusion that rice produced in Sri Lanka does not contain arsenic.

The Island - Chronic renal failure: Thousands are affected (dated January 4, 2012)

The total number of affected individuals is unknown, but it is thought that around 10,000 people, most of them in North Central Province (NCP), are currently undergoing treatment for this disease.

- CKDU is more prevalent among men, typically around the age of 40-60 years, engaged in agriculture.
- It is a major health problem in a number of DS Divisions, for example, Medawachchiya, Kahatagasdigiliya in the North Central Province. Around 1,500 people in the NCP have reached the end stage of CKDU.
- CKDU is attributed to a toxic element/s or compound/s in drinking water. Among these constituents are Cd, F, Al, toxins released by Blue Green Algae, pesticides etc.

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- 158 *Review of Literature on Chronic Kidney Disease of Unknown Etiology (CKDu) in Sri Lanka*. Andrew Noble, Priyanie Amerasinghe, Herath Manthrilake and Sutharsiny Arasalingam. 2014.
- 157 *Hydrogeology of the Eastern Ganges Basin: An Overview*. N. Rajmohan and S. A. Prathapar. 2013.
- 156 *Rapid Assessment of Water Availability and Appropriate Technologies for Small-scale Farming: Guidelines for Practitioners*. Andrew Keller, Elizabeth Weight and Stuart Taylor. 2013. (Also available in French)
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ISSN: 2012-5763
e-ISSN: 2478-1134
ISBN: 978-92-9090-788-6