Further to the previous reports (June & October 2011), during the last three months additional progress has been made in research on chronic kidney disease of uncertain aetiology, in North Central and Uva Provinces in Sri Lanka within the framework of the National Research Programme.

Overall, the results up to now indicate that long-term exposure to several risk factors toxic to the kidney in causing kidney damage in people residing in the North Central and Uva Provinces. While nephrotoxic agrochemicals and cadmium may have a direct toxic effect on the kidney, arsenic, lead, genetic factors, and others (calcium and magnesium) can have interactive effects which can indirectly damage the kidney.

In the urine analysis of 496 cases of CKDu, 56% had a urine cadmium excretion over 1 ug/g creatinine. Data from recent studies show that changes of early kidney damage occurs at cadmium excretion levels of even 0.6-1 ug/g creatinine. About 63% of CKDU patients had urine arsenic levels above 21 ug/g creatinine. Urine arsenic levels above 21ug/g creatinine have been shown to cause changes in kidney tissues that lead to chronic kidney disease. Approximately 88% of CKDu patients had urine cadmium >0.6 ug/g and/or urine arsenic >21 ug/g.

Arsenic was also analysed in hair and nails of people living in NCP including CKDu patients. In about 90% arsenic levels in hair were higher than those observed in developed countries (>0.02 ug/g). In about 94% arsenic levels in nails were higher than those observed in developed countries (>0.03 ug/g).

Our analysis did not find very high levels of cadmium exposure as reported in previous studies. The mean exposure for adults is at borderline of Recommended Total Weekly Intake (TWI) of 2.5 ug/kg body weight. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the TWI. The data for arsenic are not available yet.

Among the patients with CKDu recruited for the clinical trial with a confirmed diagnosis of CKDu about 15% had a family history of CKDu in a sibling or parent. Although current knowledge has not evolved for direct public health application, there are several genes that confer tolerance to heavy metals which are responsible for both common and specific defence mechanisms which protect cells from arsenic and cadmium toxicity. Tolerance and detoxification mechanisms often involve extrusion of the toxic ions from the cell,
sequestration within internal organelles, chelation by metal-binding proteins, and reduction of uptake.

Water from 98 water sources used by patients with CKDu was analysed for hardness. 99% are hard to very hard. Hardness of water is known to affect heavy metal toxicity through antagonistic mechanisms and this may play a role in renal toxicity caused by cadmium and arsenic in the North Central Province.

The laboratory in Antwerp has experienced difficulties in digestion of soil and fertilizer samples to determine content of heavy metals accurately and reliably and results of these analyses are still not available.

Recommendations

1. Implement the recommendations in previous reports (June 2011 and October 2011)

2. Strengthening the institutional arrangements for the implementation, inter sectoral coordination, monitoring and evaluation of control of pesticides and fertilizer. Pollution of environment with agrochemicals cannot be controlled by a single agency. Control activities should include necessary amendments to existing legislation, regulation and processes and control measures should be monitored using sensitive indicators.

3. Increasing the public awareness of the adverse health effects of agrochemicals. The general public should be made aware of the actions taken to control agrochemicals and the importance of applying safety and control measures. Health education programmes should focus on high risk populations including farmers, vendors and also expanded to involve school children and the public at large.

4. Strengthen water purification schemes in the North Central Region: Some studies have shown a weak inverse relationship between water hardness and cardiovascular disease up to a level of 170 mg calcium carbonate per litre of water. The World Health Organization has reviewed the evidence and concluded the data were inadequate to allow for a recommendation for a level of hardness. Recommendations have been made for the maximum and minimum levels of calcium and magnesium in drinking water, and total hardness.

5. As there are 66 ayurvedhic prescriptions that contain Aristolochia. Aristolochia increase awareness of Ayurvedhic Practitioners and the public of renal toxicity of Aristolochia species.
Mission Report, 6-8th June 2011
Chronic Kidney Disease of Uncertain Aetiology (CKDu), Sri Lanka

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Background
Chronic kidney disease has emerged as an important public health problem in some parts of Sri Lanka. Diabetes and hypertension contribute to this chronic kidney disease burden. However, a significant proportion of cases of chronic kidney disease that occur in the North Central and Uva Provinces are caused by a hitherto undetermined cause (Chronic Kidney Disease of Uncertain aetiology - CKDu). In order to address this public health issue, the Ministry of Health Sri Lanka in collaboration with the World Health Organization initiated a comprehensive National Research programme on CKDu in 2008/2009. Up to now this programme has been funded by the World Health Organization and the National Science Foundation of Sri Lanka.

Results of the National Research Programme
Results from Phase 1 of this research programme reveal, that in the North Central and Uva Provinces, a minimum of 15% of people in the age group 15-70 years are affected by CKDu. Men over the age of 40 years, who are engaged in farming for more than 10 years, are at a higher risk of developing this disease. In addition, exposure to agrochemicals also increases the risk of developing CKDu. The majority of men and women suffering from this disease excrete raised levels of arsenic and/or cadmium in the urine. This indicates consumption of arsenic and cadmium in either water or food. Studies done so far on (drinking) water samples from Anuradhapura, Polonnaruwa and Badulla show that cadmium and lead levels are within normal limits. Few water samples, (3 out of 118 tested), showed slightly high arsenic levels and are been reanalyzed. Within the next 6 months data will be available on the cadmium and arsenic content in samples of a) human tissue, b) water from tanks and tube wells c) food items and d) soil and fertilizer collected from the North Central Province and control areas.

Conclusions
Exposure to a combination of factors that are toxic to the kidney (rather than one single factor) seems to cause this kidney disease. Toxic factors identified up to now include, nephrotoxic agrochemicals, arsenic and cadmium. Genetic factors and other known risk factors of kidney disease appear to increase the individual susceptibility to this triple threat. Several other predisposing factors that may contribute to the development of this disease
are under investigation. The social and economic impact of CKDu on impoverished households is grave.

**Recommendations**

Based on the above findings and the progressive nature of this serious disease for which there is no cure, the following interim measures are recommended:

1. Develop a regulatory framework to improve the quality control of imported fertilizer particularly with regard to nephrotoxic agents such as cadmium and arsenic.

2. Implement measures to reduce the exposure of farmers to the harmful health effects of agrochemicals through i) health education ii) compulsory provision of safety clothing, gloves and masks at the point of sale of agrochemicals and iii) control of the sale of agrochemicals which are known to be nephrotoxic e.g. propanil, chlopyrifos and others.

3. Disseminate health education messages to people living in these areas e.g. to thoroughly wash vegetables and rice before cooking, to boil these food items in excess water and to discard the excess water once the food is cooked.

4. Increase the financial assistance provided to farmer families affected by CKDu to prevent them from getting more impoverished.

5. Provide more funds to expand and fast-track this National Research Programme of major public health importance.

It is imperative that the above steps are taken as soon as possible. Delaying action will cause further accumulation of toxic agents in the environment and result in cumulative damage to the health of the people living in these areas.