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LETTER TO THE EDITOR

Escalating chronic kidney diseases of multi-factorial origin (CKD-mfo) in Sri Lanka: causes, solutions, and recommendations—update and responses

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Author responses

Dear Editor *EHPM*:

Thank you for the Letters to the Editor in response to the above-mentioned review article published in November, 2014 in *EHPM*. I wish to address these individually:

1. Letter from Professor Oliver Illeperuma

I appreciate the thoughtful letter from Professor Illeperuma and his focussed commentaries on (A) the usefulness of the review in *EHMP*; (B) the critical evaluation in the review of the roles of all proposed potential causative factors and the "multi-factorial" nature of the disease; (C) the scientific rejection of the flawed glyphosate hypothesis; (D) the use of the most appropriate terminology for the disease—"CKD of multi-factorial origin" [CKD-mfo], and (E) identifying the potential roles of fertilizer and the Mahaweli diversion, etc., in Sri Lanka, in the multi-factorial concept of causation of CKD-mfo [1–4].

Professor Illeperuma is the originator of the hypothesis of the association between fluoride and CKD-mfo [5]. He confirmed that data and detailed maps of Sri Lanka on the distribution of fluoride, hard water, and the prevalence of CKD in the North Central Province (NCP) and elsewhere have been available for more than a "decade". This independently refutes the claims made by Drs. Jayasumana and Siribaddana. The overlaps of groundwater fluoride content and the distribution of the prevalence of CKD-mfo that Professor Illeperuma and others elegantly illustrated provided evidence of an "association", but are not sufficient yet to establish causation [6–11].

I also agree with the comments by Professor Illeperuma on the negative socio-medical-economic impact of CKD-mfo in Sri Lanka [2, 3], which has been ignored by the authorities and, is largely underestimated. Failure to address this will have a detrimental socio-economic impact in the country for years to come [1–3]. The problem is compounded by egos and conflicts of interest, and the lack of understanding about the disease among various groups, including government departments and ministries that failed to implement programmes proposed by this author and other reputed scientists, globally, over the past several years. The programmes recommended by the author include focussing on early identification of the disease using appropriate screening methods (i.e. using tubular-specific urine markers), provision of clean water to all affected and surrounding villages, broader environmental protection, and countrywide real-time surveillance programme, and actions leading to the elimination of CKD-mfo from Sri Lanka. However, fundamental issues, myths and misguidance, and obstructions must be overcome before progress can be made in preventing this disease.

2. Letter from Drs. Jayasumana and Siribaddana

Thank you for the opportunity to respond to the letter from Drs. Jayasumana and Siribaddana, who are in the habit of writing letters to the editor and anyone that argue against scientific writings that disagree with their hypothesis that glyphosate causes kidney failure. There is no scientific evidence for such a theory, and the publication by

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Jayasumana et al. offered no analytical data regarding levels of glyphosate in water bodies in any areas affected by chronic kidney disease of unknown origin (CKDuo).

To date, the cause of CKD-mfo is unknown

Even after a decade of research by various scientific groups within and outside Sri Lanka, the causes of this deadly, interstitial-tubular renal disease remain unknown [1, 2, 7]. All scientific evidence available to date including the WHO study [6–10], points to the involvement of multiple factors related to water pollution in precipitating this particular type of renal failure [1–3, 12], which further supports the correct terminology for this disease, as CKD of multifactorial origin (CKD-mfo).

The use of the right terminology: CKD-mfo

The quantities of proposed chemical contaminants reported to date in food and in small numbers of water samples analysed by various scientific groups are inadequate for the exposed individuals to contract renal failure of this magnitude [1]. Considering a number of facts, it is logical to term the disease "CKD-mfo" until a definitive cause(s) is identified, which may take another decade or more [1, 2].

Considering the complexity of issues related to CKD-mfo, this open-minded approach not only would facilitate critical thinking among researchers, but also encourage in-depth testing of broader hypotheses, a path that is more likely to identify the cause(s) than examining narrow and single-cause hypotheses. Thus, I reject narrow hypotheses and terminologies. Two writers' attempts to rename this disease as "agricultural nephropathy" or "agrochemical nephropathy" (or even fluoride or iconicity-induce nephropathy) is futile. These narrow approaches especially in the absence of valid scientific data would: (A) mislead the readership and the scientists; (B) harm ongoing CKD-mfo research programmes and protocols, and (C) misdirect the funding into non-related subjects, such as glyphosate for which credible scientific evidence does not exist. Thus, "CKD-mfo" is the most logical, and the best terminology to be used for this disease until causes has/has been identified, which may take many more years. At that point, a specific term for this disease should be applied.

Water analysis data are not conclusive

The water analysis data with reference to the levels of various components (reported and unreported) that may contribute to CKD-mfo are from public domain sources [6–10, 13], various government departments, and the author's own data. These include the analysis of agrochemicals and heavy metals data that are not distributed uniformly across the regions affected by CKD-mfo; these data are non-conclusive. This is in part due to small sample sizes, sampling and statistical errors, timing of the sample collections, and the heterogeneity of distribution of chemical components in water in regions affected by CKD-mfo in Sri Lanka. Therefore, one cannot make categorical conclusions based on relatively smaller sets of heterogeneous and uncontrolled water analysis data. Consequently, in the *EHPM* review article, I opted to discuss all published hypotheses and data, and evaluated these critically and succinctly for the benefit of the readers [1].

Additive or synergistic interactions of chemicals causing CKD-mfo

One cannot extrapolate the experiments conducted in a test tube in a laboratory to what is happening in vivo in animal or human bodies. It is easy to demonstrate synergy between chemicals and components in laboratory experiments, but difficult to design studies to demonstrate such in in vivo situations of multiple potential interactions. Therefore, one cannot disregard the potential synergistic interactions between chemicals in vivo that lead to renal failure, when hundreds of such chemicals, factors, and conditions come into play.

Those who are not involved directly in medical research may not be familiar with the fact that these in vivo inter-compound interactions lead to various human diseases and organ failure. It is also a common practice in medicine to use less-than-optimum amounts (or lower than the effective dose) of two or more agents to treat diseases (e.g. heart disease, hypertension, asthma, diabetes, etc.) utilizing their synergy; this is done to enhance the synergy, avoid adverse effects of individual medications, and to reduce costs [14]. There are dozens of human conditions for which additive or synergistic effects of various chemicals, compounds, or components precipitate a syndrome, disease, or organ failure; chronic renal failure is not unique in that sense.

No published studies have attempted to assess or incorporate into hypotheses or carried out experiments to demonstrate the "real" interactions and synergistic effects of different components in vivo on renal tubular damage (at least in vitro, organ culture systems) of CKD-mfo. Figures 2 and 3 in the *EHPM* review article were based on the knowledge that we had in early 2014 [1] and illustrate, most if not all, postulated causes of the disease, with the author keeping an open mind and providing a balanced analyses to the readership.

Prevalence of CKD-mfo

The current prevalence of total CKD patients among the adults in the NCP is about 12.5 %, whereas the prevalence of renal failure caused by CKD-mfo is approximately

7.5 % [1, 3]. The difference is attributable to CKD of known causes, namely hypertension and type 2 diabetes (T2D). In their letter to the BMC-Nephrol [6], the two writers criticized the WHO Group's research and the WHO final report [7]. Contrary to their criticism, the WHO report contains noteworthy information regarding pesticides and the herbicide glyphosate. To date, in no research study in Sri Lanka have the components of glyphosate or postulated heavy metals in water been detected or reported in appreciable or clinically meaningful amounts [6–8].

I have been working on water quality and issues related to CKD-mfo in the CKD-mfo affected regions in Sri Lanka since 1998 and have provided several written proposals to the Ministry of Health with detailed recommendations for the prevention and eradication of CKD-mfo in the NCP region and the country. The first such formal proposal was made in 2006, followed by proposals in 2009, 2011, and 2012. Moreover, my article in *EHMP* [1] was previously submitted to another journal in February 2013, long before the unproductive, "National Project for Prevention of Kidney Disease" (NPPKD) was established in mid-2014, and the NPPKD Website description that was mentioned by Dr. Jayasumana must have appeared after that.

The spread of CKD-mfo in the country

Drs. Jayasumana and Siribaddana provide inaccurate percentages for paddy cultivation areas in Sri Lanka, and the Websites and newspaper articles they have cited in support of their claims are not authoritative. These writers do not seem to understand that the disease continues to spread outside the traditional boundaries of the NCP and the North Central Region (NCR) into adjacent and distant areas in the country. In addition, their characterization of the prestigious, national, annual, Col. Olcott Oration in Sri Lanka as a high school lecture is regrettable [4].

Sub-standard screening/diagnostic methods leading to under-diagnosis

For a number of reasons, as described in the *EHPM* review article, the disease prevalence and deaths related to CKD-mfo are markedly underestimated by the ministry of health. Moreover, the current criteria and methodology recommended and widely used by the Department of Health for screening and diagnosis of this disease [7, 15], including the use of urinary albumin or microalbumin/creatinine ratio identifies less than 35 % of those with CKD-mfo [16]. Unfortunately, many patients diagnosed with CKD-mfo using currently recommended screening procedure, kidney disease has extended beyond CKD stage 3b (i.e. irreversible stages).

Because of the lack of sensitivity of the screening methods used, in an overwhelming majority of patients, the diagnosis of CKD-mfo is made too late. This prevents the ability for reversing the renal impairment, decreasing the need for renal dialysis, and preventing premature deaths. The current proposal to decrease the urine microalbumin/creatinine diagnostic cut-off from 30 to 10 mg, may improve the detection rate to as much as 50 %, which is still not sufficiently sensitive enough to make a meaningful early diagnosis [17]. On the other hand, the use of highly sensitive and specific renal tubular-specific markers (none of which are used in Sri Lanka yet) would increase the sensitivity and specificity, with a detection rate greater than 85 %. This would enable healthcare workers to identify those patients with CKD-mfo at an early stage [i.e. stages below 3a] [18], providing an effective opportunity to reverse renal impairment and thus [16], curtailing the need for dialysis and preventing premature deaths [17].

CKD-mfo deaths are grossly under-reported

The cause of death in patients dying of CKD-mfo is often mis-documented for a variety of reasons, including political reasons and cultural factors, and stigma, leading to significant under-documentation of deaths attributable to CKD-mfo [1, 3, 17]. For example, in many instances, families of the victims insist that the cause of the death not be identified as CKD-mfo [4], primarily because of the associated stigma for the family, including potential difficulties in giving their children in marriage.

Role of heavy metal in CKD-mfo

Published data are inconsistent, in part because of non-standardized sample collections, small sample sizes, and non-systematic sample collections, the timing of collections (especially with regard to proximity to period of rain and droughts), and the variation in analytical methodologies used. The lack of strength of these unconfirmed, pilot data neither support nor categorically exclude the involvement of agrochemicals, fluoride, or heavy metals (arsenic, cadmium, lead, etc.) as a cause of CKD-mfo [1, 2, 6–8]. However, these postulates, including pH of water, volatile components in soil, air, and water, etc., and other susceptibilities in various levels in combination, in quantities lower than those do considered necessary to cause renal tubular damage may play a role in causing the disease. This is an example of the multi-factorial nature of this disease.

Glyphosate and renal failure

I agree with many scientists [19] that there is no rationale or scientific basis for the suggestion of Jayasumana and colleagues that glyphosate causes CKD-mfo. With reference to this, I would like to point out a typographical error in the

EHPM review (page #11): "However, *none* of the published data including the WHO report *failed* to identify detectable amounts of agrochemicals including glyphosate in water." Indeed, the text should read as, "However, none of the published studies have identified appreciable or meaningful amounts of glyphosate in water" [6, 7]. In addition to my assertion, several independent scientists also addressed this matter thoroughly elsewhere and have rejected the suggestion that glyphosate causes CKD-mfo [19–21].

Conceptual errors and insufficient scientific data

The two writers unfairly criticized the dearth of primary data in this review article. Apparently, they are unaware that in a scientific review article, it is not customary or necessary to provide primary sets of data.

In affluent societies and in major cities, the prevalence of T2D and abdominal obesity are higher than in villages and rural communities because of unhealthy eating habits and sedentary lifestyles and multiple environmental issues. In the clinical study quoted in their letter to justify their views of the prevalence of diabetes in the NCP region [SLJDEB, 2011;1:2–7], data were collected from city inhabitants in the western province, the capital of Sri Lanka. However, considering that approximately 70 % of Sri Lankans live in villages, the countrywide prevalence of T2D is not significantly different in the NCP region compared with the rest of the country. Scientifically, it is misleading to compare data obtained from a handpicked small community against a region populated with more than 2 million to defend a point of view.

In the past 5 years, Dr. Jayasumana has speculated the cause of CKD-mfo to be: (A) poisoning of the region by a former terrorist group; (B) arsenic or lead; (C) cadmium; and most recently, (D) glyphosate. However, no credible data were presented to support any of these hypotheses. In India and Bangladesh, there are reports of association between arsenic and chronic renal failure, but no such scientific evidence is available for Sri Lanka. No credible scientific data have been published anywhere in the world that support glyphosate causing chronic renal failure or CKD-mfo.

The sparse data published with reference to arsenic, cadmium, and glyphosate are weak and unsystematic, and thus have been disregarded by scientists [6–10, 13]. Therefore, contrary to the statements by the two writers, there is no convincing scientific data from Sri Lanka that arsenic, cadmium, lead, or glyphosate causes CKD-mfo [4]. In fact, there are no reports from any scientific groups other than Jayasumana and colleagues on arsenic, lead or glyphosate causing CKD-mfo. In addition, the two writers say that in their article in *J. Environ. Res. Public Health* about glyphosate, they explained the heterogeneity of the geographical distribution of patients with CKD-mfo; this is another assertion that is not supported by careful reading of the article.

False claims

The Website cited by Drs. Jayasumana and Siribaddana in their letter (ref. #10) shows an article by an independent journalist: (http://www.island.lk/index.php?page_cat=article-details&page=article-details&code_title=97368) that provides no relevant information to the subject of discussion. Meanwhile, it seems likely that the NPPKD may have adopted some of the recommendations made by me over the past several years.

The two writers' arguments about the maps in the *EHPM* review article (Figure 1; [1]) are meaningless (-please also see the comments made above by senior Professors, Illeperuma and Fernando in their Letters to the Editor, this regard). For several years, the data related to the distribution of hard water, fluoride, CKD-mfo disease prevalence, etc., have been available from the National Water Resources and Drainage Board, Institute of Fundamental Studies in Sri Lanka, and other sources, and I have also collected data during the past four decades. In fact, Professors, Oliver Illeperuma and Ravindra Fernando independently confirmed the availability of these data for many years, in their Letters to the Editor.

For a decade, scientists, including me, have used the publically available data (and my own data) to create distribution maps [4]. These two writers were not the first to create such maps; they have adapted these from others. Moreover, the incidence of CKD-mfo is doubling approximately every 4 years in this region [2, 3]; therefore, in addition to the real-time surveillance programme, constant updating of the dispersal maps is needed using the GIS locations and other means to keep the CKD-mfo prevalence and vulnerability data accurate.

3. Letter from Professor Ravindra Fernando

The letter by Professor Ravindra Fernando concisely identifies some of the important contributions I have made to the field of chronic kidney disease of multi-factorial origin (CKD-mfo) in Sri Lanka during the past 16 years. These contributions identified include: (A) unbiased discussions of postulated contributing factors to this disease while remaining open to new valid ideas; (B) critical evaluation of potential roles of heavy metals, aristolochic acid, infectious aetiology, dehydration, agrochemical and pesticide exposure, etc. (also illustrated the usefulness of the Figures 1, 2, and 3 in the *EHPM* review); (C) dissemination of unbiased educational information and knowledge to readers and public using various multimedia; (D) scientific rejection of the flawed glyphosate hypothesis

that has misled the public and the government, and (E) coining the use of appropriate terminology [CKD-mfo] for this disease [1–3].

He also touched on the fact that despite the millions of rupees spent on research, no cause(s) of CKD-mfo has/have been identified. This is in part because of the narrow scope and hypotheses of research protocols that have been studied and the use of non-standardized research protocols [1]. Most importantly, as an established senior toxicologist—a medical researcher, Professor Fernando understands the potential involvement and importance of "multiple factors" and their possible synergy in precipitating critical organ damage [22], including kidney failure and the development of CKD-mfo [1–4]. In addition, he independently confirmed that the data and maps on the prevalence of CKD-mfo and the distribution of hard water in Sri Lanka have been available since early 2000, completely refuting claims by Dr. Jayasumana.

I agree with Professor Fernando that many of the currently postulated hypotheses of potential causes of CKD-mfo, including glyphosate, fluoride, heavy metals, aristolochic acid, illegal alcohol, tobacco, ionicity, and infectious aetiology, have been made without scientific evidence or credible experimental data [1, 4–6]. This further emphasizes the importance of implementing a nationwide, real-time surveillance programme and a well-coordinated, broad multi-disciplinary, long-term research programme to identify and eliminate CKD-mfo from Sri Lanka. I sincerely hope that these will materialized in the near future.

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