

# Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? CON

Catharina Wesseling <sup>1,2</sup>

KIDNEY360 1: 596–601, 2020. doi: <https://doi.org/10.34067/KID.0002922020>

## Introduction

Over the last three decades, tens of thousands of premature deaths due to CKD of nontraditional origin (CKDnt) (The Pan-American Health Organization recommends the use of CKDnt in the Americas (1) <https://www.paho.org/hq/dmdocuments/2015/CE156-INF-8-e.pdf> and I use this term in this document) have occurred in Mesoamerica's Pacific coastal areas, the Northern Central Province of Sri Lanka, and Uddanam, India. Toxins and occupational heat stress are the two main hypotheses for primary causes (2,3).

I present arguments in favor of a heat stress nephropathy in contrast to a toxic nephropathy. My case is presented on the basis of (1) the need for well designed epidemiologic studies, (2) the reasons why a primary toxic cause of CKDnt is unlikely, and (3) a summary of the evidence for occupational heat stress as the prime driver of CKDnt in Mesoamerica, recognizing that heat stress has not yet been explored in Sri Lanka or India (Table 1).

## Strong Epidemiology Needed

Finding a cause for an epidemic is a different research scenario from establishing associations between hazards and subtle disease occurrence. An epidemic implies many affected people and a strong driver, be it a biologic, chemical, or physical hazard. Any presumed risk factor must be highly prevalent in the most affected subpopulations and be specific to them. To unravel the cause of the CKDnt epidemics, well designed epidemiologic prevalence and analytical studies are essential, revealing the distribution of CKDnt in different populations and linking adequate exposure data of any potential hazard to the disease's occurrence. Epidemiology should be consistent with social science, physiology, toxicology, and pathology studies, but without documented epidemiologic associations no reasonable causal assertions can be drawn.

Although seemingly obvious, when it comes to providing proof of CKDnt cause such principles are often overlooked. Solid epidemiologic research has been mostly developed in Mesoamerica, is largely missing in Sri Lanka, and only about to start in India. Causal assertions around CKDnt are too often on the basis of "ecological" assumptions (see Table 1). Although some

researchers have named the regional CKDnt epidemics collectively "Chronic Interstitial Nephritis in Agricultural Communities (CINAC)" (3–5), the evidence is simply inadequate to conclude that the clinical, pathologic, and epidemiologic features of CKDnt in Mesoamerica, Sri Lanka, and India are identical, or that they have a common source such as agrochemicals. The fact that agricultural work is common in the rural areas where the epidemics predominate is not evidence of an agrochemical cause. Nor is the absence of reports from hot areas of the globe evidence that the cause is not related to excessive heat. Geographical and time trend correlations are, at best, hypothesis-generating. Even perfect correlations can be subject to the "ecological fallacy" (9).

## The Low Probability of a Primary Toxic Cause

Pesticides and metals are the two main types of toxic agent that have been suggested to be causes of the CKDnt epidemics (2,3,10–12).

Assessments of associations of "pesticides" with kidney disease are abundant in the literature (6) and are used in meta-analyses of CKDnt as if it was a valid exposure indicator (13,14). However, the term "pesticides" includes any of hundreds of active ingredients, each with their own distinct toxicities. Their uses vary markedly over regions, crops, and time (6). Can we learn anything from an exposure assessment that is so general and nonspecific?

Studies in nonendemic/epidemic regions have found adverse kidney effects arising from exposure to pesticidal active ingredients (6), including ESKD from occupational exposures to common-use herbicides like atrazine and paraquat (but not glyphosate) among licensed pesticide applicators in the USA (15), and CKDnt from environmental (dietary) exposures to organochlorine insecticides in urban Delhi (16). Such studies have been repeatedly cited in support of the pesticide hypothesis for CINAC (4,5), but, to confirm an association to CKDnt epidemics, a relationship between exposure and outcome must be demonstrated in a population at risk for CKDnt. Proper epidemiologic studies are lacking (6). One exception is a community cohort in a CKDnt hot spot in Nicaragua, where baseline urinary levels to 12 pesticides, including

<sup>1</sup>La Isla Network, Washington, DC

<sup>2</sup>Unit of Occupational Medicine, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

**Correspondence:** Catharina Wesseling, La Isla Network, Unit of Occupational Medicine, Institute of Environmental Medicine, San Jose, Costa Rica. Email: [inekewesseling@gmail.com](mailto:inekewesseling@gmail.com)

**Table 1. Arguments at a glance**

Arguments	Arguments Against
<p><b>Epidemiology</b></p> <p>Without robust epidemiologic evidence, there can be no progress on causal knowledge <i>Hazard × exposure = risk</i></p> <p>Too much causal thinking on the basis of “ecological” observations and assumptions, subject to “ecological fallacy”</p>	<p>Well designed epidemiologic studies are essential for establishing risks and causes:</p> <p>Strong epidemiologic evidence exists for occupational heat stress in Mesoamerica</p> <p>No clear positive epidemiologic findings exist for pesticides or metals in any of the three regions.</p> <p>Ecological fallacy: Making inferences about risks in geographical areas or time periods without knowing individual exposure, outcome, and covariate distributions in study populations</p> <p>Hypothetical example applied to CKDnt: Regions with high and low pesticide use have, respectively, high and low CKD mortality. Inference: CKD mortality is caused by high pesticide use, which is a meaningless conclusion in case of coexistence of high pesticide use and frequent demanding manual work in hot climate.</p>
<p><b>Primary toxic cause</b></p> <p><b>Pesticides PRO arguments (3–5)</b> “Identical” CKDnt epidemics in three agricultural regions with high pesticides use: CINAC <i>Certain globally ubiquitous active ingredients are of special interest, for example glyphosate, paraquat, and several organophosphates and pyrethroids</i></p> <p>CKDnt clinical emergence in the 1990s coincides with rapid increase in pesticide use</p> <p>Higher prevalence of kidney dysfunction in men relates to occupational pesticide use</p> <p>CKDnt or kidney injury markers among nonworking women, children, and adolescents is explained by environmental pesticide exposure pathways of inhalation and dermal absorption from drifts, and consumption of contaminated food and water</p> <p>“Pesticides” as a collective toxic exposure indicator</p> <p>Associations between specific active ingredients and kidney dysfunction outcomes, in regions not affected by CKDnt</p>	<p><b>Pesticides CON arguments</b></p> <p>Pesticide use is high in countless agricultural regions without CKDnt, around the globe.</p> <p>Use varies markedly over crops, regions, and time, even for widely used pesticides: the presence of any specific putative pesticide in all epidemic regions during decades of epidemic is unlikely.</p> <p>Prevalence of kidney dysfunction is high also in nonagricultural communities in Nicaragua: a mining region and a semiurban area with brickmaking industry, unexposed to pesticides.</p> <p>Potential associations between ubiquitous pesticides and CKDnt can only be determined in the populations at risk for CKDnt. Such studies have been negative so far: In El Salvador cane cutters at high risk of CKDnt: urinary levels of glyphosate and 2,4-D were negligible. In Nicaraguan community cohort in CKDnt hot spot: no associations were found between baseline urinary levels of 12 common-use pesticides and rapid kidney decline.</p> <p>Comprehensive reviews of pesticides and CKDnt did not find relevant associations.</p> <p>In Central America, excess CKD mortality in epidemic regions emerged in the mid-1970s.</p> <p>Men who are workers can also be exposed to hazards other than pesticides. In epidemic areas of Nicaragua and El Salvador, kidney dysfunction concentrates among workers in industrial agriculture, with cane cutters at highest risk the least exposed to pesticides, and subsistence farmers with higher pesticide exposures being far less affected.</p> <p>Worker populations unexposed to pesticides are also affected: mining, construction, brick makers, and others.</p> <p>Population-based prevalence studies in El Salvador and Nicaragua show: Kidney dysfunction is infrequent in economically inactive populations, for both men and women. High men:women ratios in endemic areas are not in accordance with an environmental toxic cause.</p> <p>Women and children in Mesoamerica are poorly studied, and studies have weak design, lack measurement of presumed environmental pesticide exposures, and lack assessment of child labor (early heat stress).</p> <p>Chronic diseases are all multifactorial; contributory factors do not exclude occupational heat stress as main driver.</p> <p>“Pesticides” are a toxicologically heterogeneous group with dozens of chemical families, hundreds of active ingredients, and thousands of commercial formulations with different “inert” ingredients.</p> <p>Associations between nephrotoxic pesticidal active ingredients and adverse kidney effects are to be expected in epidemiologic studies, but unrelated to CKDnt epidemics.</p> <p>Potential associations between nephrotoxic pesticides and CKDnt epidemics can only be determined in the populations at risk for CKDnt.</p>

Table 1. (Continued)

Arguments	Arguments Against
<p>Occupational and environmental exposures to pesticides is the likely underlying cause of CINAC through calcineurin pathway inhibition or modulation (5), analogous to kidney effects of immunosuppressive drugs in transplant patients</p>	<p>The CINAC calcineuron inhibition (CNI) hypothesis is based on ecological thinking.            There is no epidemiologic evidence of pesticides related to CKDnt epidemics (all of the above reasons).            Direct experimental evidence of pesticides being CNIs is nearly inexistent. Whether common-use pesticides are important as CNIs must be tested experimentally.            Any associations between suspected CNI pesticides and CKDnt epidemics need to be established through well designed epidemiologic studies.</p>
<p><b>Metals and toxic mixtures PRO arguments</b>            A number of metals are nephrotoxic and have caused epidemics historically (e.g., cadmium in the food chain and itai-itai disease in Japan)            Mixtures of ubiquitous environmental toxins may cause CKDnt epidemics</p>	<p><b>Metals and mixtures of toxins CON arguments</b>            Clinical and pathologic characteristics of CKDnt are not in accordance with the known renal clinical effects of cadmium, lead, mercury, arsenic, lithium, or uranium, nor with well established dose-effect and dose-response relationships.            The existence of specific mixtures of low-dose toxins covering large geographic areas in different countries and with potent nephrotoxic effects is unlikely.</p>
<p><b>Occupational heat stress as primary cause in Mesoamerica</b>  <b>Heat stress CON arguments (3-5)</b>            Increases in temperature due to climate change in CKDnt affected regions seem insufficient for epidemics of heat stress nephropathy. There are many hot regions in the world without CKDnt. It has always been hot. Why would CKDnt manifests itself until now? Heat stress has not been identified as a causal factor for CKDnt in Sri Lanka or India. In Sri Lanka, the Northern Central Province with the hottest climate does not report CKDnt. In Sri Lanka, at the time the CKDnt epidemic started, rice paddy farmers at highest risk mechanized the harvesting process, reducing their heat stress.</p>	<p><b>Occupational heat stress PRO arguments</b>  <i>It is possible that causal factors and underlying physiopathologic mechanisms are not the same for the different regions with CKDnt epidemics.</i>            All CON arguments are "ecological" in nature. Yet similar PRO "ecological" arguments exist:            Excess kidney dysfunction is quite consistently found in lowlands in the equatorial belt, among young laborers in hot places with poor labor protections and hard physical work.            Occupational heat stress derives from the combination of extreme physical workload in high environmental temperatures. Hence, not all hot regions will be equally affected.            Excess kidney dysfunction is NOT consistently found in places with high pesticide use, which exist globally from the very north to the very south, in lowlands and highlands, in all continents            Climate change has coincided with the green revolution and increasing pesticide use, but also with profound economic changes and transition from subsistence farming to industrialized agriculture:            Less control over physical work demands, piece rate payments, and loss of nutritional subsistence crops.            Heat stress in relation to CKDnt has not been addressed in Sri Lanka or India            In well designed epidemiologic studies, heat stress should be measured objectively during harvest and nonharvest seasons, along with markers and changes in kidney function.</p>
<p><b>Strong epidemiologic evidence of occupational heat stress underlying the CKDnt epidemic in Mesoamerica</b>  <i>Prevalence and cohort studies:</i>            Sugarcane field workers, especially cutters, have been identified as populations at high risk for CKDnt, as well as workers in other hot jobs.            Heat measurements in the field among cane cutters show high internal and external heat.            Cross-shift studies show changes in kidney function and hydration parameters during cane cutting indicating heavy load on the kidney.            Crossharvest declines in kidney function are most severe and incident kidney injury is most frequent among manual laborers with the highest physical workload.            Incident kidney injury during the sugarcane harvest season associates with markers of physiopathologic mechanisms related to heat-induced inflammation.  <i>Intervention research:</i>            Reduction in heat stress through water-rest-shade programs leads to reduction in kidney damage</p>	
<p>Many studies referred to in this table are included in recent reviews (2-4,6-8). 2,4-D, 2,4-dichlorophenoxyacetic acid; CINAC, chronic interstitial nephropathy of agricultural communities; CKDnt, CKD of nontraditional origin; CNI, calcineurin inhibitor.</p>	

glyphosate and pyrethroids, did not associate with rapid kidney function decline (17).

A recent pathology study hypothesized that glyphosate, paraquat, and pyrethroids are calcineurin inhibitors underlying CINAC, on the basis of the finding of aberrant lysosomal structures in proximal tubular cells of CINAC patients that are identical to those observed in kidney

transplanted patients treated with high doses of calcineurin inhibitor immunosuppressors (5). However, such lysosomal structures are not pathognomonic and are observed in healthy transplant donors and other kidney diseases (18). Additionally, experimental data on calcineurin inhibition from pesticides are nearly inexistent, and the overall assumption is on the basis of similar "ecological" coincidences

as commented on above. In Sri Lanka, a case-control study found an association between glyphosate and CKDnt (19), but glyphosate has not been linked to kidney injury in any other study (6,7). Other common-use pesticides have also been examined as potential causal agents of the epidemic in Mesoamerica without relevant associations emerging (6,7). Importantly, and often ignored, CKDnt occurs among workers in occupations such as mining, construction, brick-making, and shrimp farming without use of glyphosate or other specific pesticides (2,8). Yet, local CKDnt outbreaks affecting men and women alike, and children, have been reported in Las Brisas, El Salvador (8) and Chapala, Mexico (20), and a potential environmental toxic cause must be investigated adequately. A toxic agent producing epidemics should be identifiable with current epidemiologic research methods and chemical analytical capacities for thousands of potential putative agents.

Regarding metals, the clinical and pathologic characteristics of CKDnt are neither in accordance with the known renal effects of lead, cadmium, mercury, arsenic, lithium, or uranium, nor with well established dose-effect and dose-response relationships (21). For a discussion with focus on CKDnt, I invite readers to read working papers presented at three international workshops on CKDnt in 2012, 2015, and 2019, which examined the role of metals (7,22,23). It was repeatedly concluded that these metals were an unlikely cause of the epidemics in Mesoamerica and Sri Lanka.

With no evident toxic candidate as a main cause, part of the CKDnt research community is now moving toward examining mixtures of ubiquitous environmental toxins (7). But how likely is the existence of specific mixtures of low-dose toxins that are widespread and with an effect so strong that they cause CKDnt epidemics covering large geographic areas in different countries?

As in all chronic diseases, multiple conditions over the course of a lifetime will ultimately contribute to the risk of getting a disease, including low-dose exposures to toxic agents. However, regarding a driver of an epidemic, it is common sense to focus on the obvious rather than speculating that unknown agents, unidentified after decades of an epidemic, are persistently killing tens of thousands of people, mainly workers.

### Strong Evidence for Occupational Heat Stress in Mesoamerica

My research group recently performed an exhaustive review of all published epidemiologic studies on CKDnt conducted in Mesoamerica up to mid-2019, approximately 30 population-based prevalence and analytical studies (8). In all nine prevalence studies that looked at high-risk areas, kidney dysfunction was 2.5–4 times more frequent in men than in women, indicative of an occupational and contrarian to an environmental cause. The data collectively leave no doubt that manual laborers, not just agricultural workers, in hot climates are by far the most affected. A few studies report CKDnt among nonworking women and children, and increased markers of early kidney injury in adolescents. Still, for Mesoamerica, any environmental toxin, or genetic or behavioral trait, considered to be a primary or contributing cause of CKDnt should be congruent with the observed occupational pattern of kidney dysfunction, *i.e.*,

much more frequent among men who are manual workers in hot jobs.

Thirteen analytical studies were conducted among sugarcane workers, a high-risk population. These studies from El Salvador, Nicaragua, Guatemala, and Costa Rica invariably pointed to kidney dysfunction being related to prolonged extreme physical workloads in hot climatic conditions leading to repeated increased core temperatures and dehydration (8). Four studies examining workers in non-agricultural “hot” occupations (mining, brick making, and construction) also observed kidney dysfunction, which supports the evidence (8). Studies on other causes, *e.g.*, pesticides, arsenic, and other metals, and importantly leptospirosis or other infections, have found no evidence to sustain these hazards as primary causes (2,8).

Noteworthy is the intervention research conducted in El Salvador and Nicaragua that provides evidence that water-rest-shade programs, when correctly implemented, reduce the incidence of kidney damage in high-risk workers (24–26). The finding that reduction of heat stress leads to a reduction in kidney damage, *i.e.*, reduction of a suspected exposure leads to less damage, is profoundly important when assessing causality, even when extended observation is still needed to verify less-manifest CKDnt.

The early focus on recurrent dehydration leading to renal dysfunction over time has shifted to increased core temperature with or without dehydration (25–27), with inflammatory responses playing a key role (28). The heat stress hypothesis is also supported by animal and human experiments (29,30) and physiology research in athletes (31). Hansson *et al.* (28) constructed a theoretical framework of possible pathophysiologic pathways for heat-induced kidney injury, on the basis of recent heat and exercise physiology literature. The theory was tested through longitudinal analyses of original data obtained from >800 sugarcane cutters followed up in the intervention studies mentioned above. The conclusion was that “pushing kidneys to the physiological limits daily, causing high tubular reabsorption demand whereas reducing blood flow, and repeating proinflammatory stimuli such as uric acid, fructose, hypoxia, cytokines, and/or endotoxins may contribute to fibrotic changes rather than successful healing.”

The link between heat stress and CKDnt has not been examined outside Mesoamerica and should be addressed in other regions. The precautionary principle and known associations with AKI and heat illness are reason enough to prevent heat stress in manual workers.

- Epidemiologic evidence must support hypotheses from any potential main driver of CKDnt epidemics. Epidemiologic data are comprehensive in Mesoamerica, weak in Sri Lanka, and just starting to be collected in India.
- In Mesoamerica, epidemiologic data do not support toxins (or infections) as a primary cause. In Sri Lanka, ample environmental research has not pinpointed any specific toxin or exposure routes.
- The evidence for heat stress as the main driver of kidney injury that could lead to CKDnt is strong in Mesoamerica and pathophysiologic mechanisms have been identified. Occupational heat stress has not been investigated in Sri Lanka or India.

- Heat stress interventions in Mesoamerica have been shown to reduce kidney injury.

#### Acknowledgments

I thank the International Research Team of La Isla Network for constructive advice.

#### Author Contributions

C. Wesseling conceptualized the manuscript and wrote the original draft and revision.

#### Disclosures

The author has nothing to disclose.

#### Funding

None.

#### References

- Pan American Health Organization, World Health Organization: CKD in agricultural communities in Central America. *156th Session of the executive committee PAHO/WHO. Progress Report on Technical Matters. CE156/INF/8. Washington, D.C., 22-26 June, 2015*, Washington D.C., PAHO/WHO, 2015, pp 17–21. Available at: <https://www.paho.org/hq/dmdocuments/2015/CE156-INF-8-e.pdf>
- Johnson RJ, Wesseling C, Newman LS: Chronic kidney disease of unknown cause in agricultural communities. *N Engl J Med* 380: 1843–1852, 2019
- Jayasumana C, Orantes C, Herrera R, Almaguer M, Lopez L, Silva LC, Ordunez P, Siribaddana S, Gunatilake S, De Broe ME: Chronic interstitial nephritis in agricultural communities: A worldwide epidemic with social, occupational and environmental determinants. *Nephrol Dial Transplant* 32: 234–241, 2017
- Herath C, Jayasumana C, De Silva PMCS, De Silva PHC, Siribaddana S, De Broe ME: Kidney diseases in agricultural communities: A case against heat-stress nephropathy. *Kidney Int Rep* 3: 271–280, 2017
- Vervae BA, Nast CC, Jayasumana C, Schreurs G, Roels F, Herath C, Kojc N, Samaee V, Rodrigo S, Gowrishankar S, Mousson C, Dassanayake R, Orantes CM, Vuiblet V, Rigother C, D'Haese PC, De Broe ME: Chronic interstitial nephritis in agricultural communities is a toxin-induced proximal tubular nephropathy. *Kidney Int* 97: 350–369, 2020
- Valcke M, Chaverri F, Monge P, Bravo V, Mergler D, Partanen T, Wesseling C: Pesticide prioritization for a case-control study on childhood leukemia in Costa Rica: A simple stepwise approach. *Environ Res* 97: 335–347, 2005
- Wesseling C, van Wendel de Joode B, Jakobsson K, Joubert BR, Lebov J, Birnbaum L, Jayasumana C, Manage P, Wanigasuriya K: Pesticides and metals. In: *Technical Report from the Third International Workshop on Chronic Kidney Diseases of Uncertain/Non-traditional Etiology in Mesoamerica and Other Regions*. Edited by Crowe J, Joubert BR, Brooks D. San José, Costa Rica, March 20–22, 2019. IRET-SALTRA-UNA, Costa Rica; National Institute of Environmental Health Sciences, National Institutes of Health, USA. pp 73–90, in press
- Wesseling C, Glaser J, Rodriguez-Guzmán J, Weiss I, Lucas R, Peraza S, da Silva AS, Hansson E, Johnson RJ, Hogstedt C, Wegman DH, Jakobsson K: Chronic kidney disease of non-traditional origin in Mesoamerica: A disease primarily driven by occupational heat stress. *Rev Panam Salud Publica* 44: e15, 2020
- Hsieh JJ: *Ecological Fallacy*, Britannica Online Academic Edition, 2020. Available at: <https://www.britannica.com/science/ecological-fallacy>
- Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D (eds): *Mesoamerican Nephropathy: Report from the First International Research Workshop on MeN*. Heredia, Costa Rica: SALTRA/IRET-UNA, 2013. ISBN 978-9968-924-06-1. Available at: [http://www.saltra.una.ac.cr/index.php?option=com\\_content&view=article&id=41&Itemid=155](http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=41&Itemid=155) (Volume 10). Accessed May 8, 2020
- Wegman D, Crowe J, Hogstedt C, Jakobsson K, Wesseling C (eds): *Mesoamerican Nephropathy: Report from the Second International Research Workshop on MeN*. Heredia, Costa Rica: SALTRA/IRET-UNA, 2016. ISBN 978-9968-924-33-7. Available at: [http://www.saltra.una.ac.cr/index.php?option=com\\_content&view=article&id=41&Itemid=155](http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=41&Itemid=155) (Volume 33). Accessed May 8, 2020
- Crowe J, Brooks D, Correa-Rotter R, González-Quiroz M, Jakobsson K, Kimmel P, Mendley S, Trottier B, Joubert B: Technical Report from the Third International Workshop on Chronic Kidney Diseases of Uncertain/Non-traditional Etiology in Mesoamerica and Other Regions. San José, Costa Rica, March 20–22, 2019, IRET-SALTRA-UNA, Costa Rica; National Institute of Environmental Health Sciences, National Institutes of Health, USA. in press
- Chapman E, Haby MM, Illanes E, Sanchez-Viamonte J, Elias V, Reveiz L: Risk factors for chronic kidney disease of non-traditional causes: A systematic review. *Rev Panam Salud Publica* 43: e35, 2019
- González-Quiroz M, Pearce N, Caplin B, Nitsch D: What do epidemiological studies tell us about chronic kidney disease of undetermined cause in Meso-America? A systematic review and meta-analysis. *Clin Kidney J* 11: 496–506, 2018
- Lebov JF, Engel LS, Richardson D, Hogan SL, Hoppin JA, Sandler DP: Pesticide use and risk of end-stage renal disease among licensed pesticide applicators in the Agricultural Health Study. *Occup Environ Med* 73: 3–12, 2016
- Ghosh R, Siddarth M, Singh N, Tyagi V, Kare PK, Banerjee BD, Kalra OP, Tripathi AK: Organochlorine pesticide level in patients with chronic kidney disease of unknown etiology and its association with renal function. *Environ Health Prev Med* 22: 49, 2017
- Smpokou ET, González-Quiroz M, Martins C, Alvito P, Le Blond J, Glaser J, Aragón A, Wesseling C, Nitsch D, Pearce N, Norman J, Lindh CH, Morton J, Caplin B: Environmental exposures in young adults with declining kidney function in a population at risk of Mesoamerican nephropathy. *Occup Environ Med* 76: 920–926, 2019
- Wijkström J, Elinder CG, Hultén K, Söderberg M, Wernerson A: “Dysmorphic” lysosomes in proximal tubular cells are not specific for CINAC/CKDu and do not provide evidence that CINAC/CKDu is a toxin-induced disease. *Kidney Int* 2020 10.1016/j.kint.2020.04.057
- Jayasumana C, Paranagama P, Agampodi S, Wijewardane C, Gunatilake S, Siribaddana S: Drinking well water and occupational exposure to herbicides is associated with chronic kidney disease, in Padavi-Sripura, Sri Lanka. *Environ Health* 14: 6, 2015
- Lozano-Kasten F, Sierra-Díaz E, de Jesús Celis-de la Rosa A, Margarita Soto Gutiérrez M, Aarón Peregrina Lucano A; Research Group on Social and Environmental Determinants in Childhood: Prevalence of albuminuria in children living in a rural agricultural and fishing subsistence community in Lake Chapala, Mexico. *Int J Environ Res Public Health* 14: 1577, 2017
- Nordberg G, Fowler B, Nordberg M: *Handbook on the Toxicology of Metals*, 4th Ed., Cambridge, MA, Academic Press, 2014
- Jakobsson K, Jayasumana C: Chronic kidney disease of unknown origin in Sri Lanka. In: *Mesoamerican Nephropathy: Report from the First International Research Workshop on MeN*. Heredia, Vol. 10, edited by Wesseling C, Crowe J, Hogstedt C, Jakobsson K, Lucas R, Wegman D, Heredia, Costa Rica, SALTRA/IRET-UNA. ISBN 978-9968-924-06-1., 2013, pp 53–56. Available at: [http://www.saltra.una.ac.cr/index.php?option=com\\_content&view=article&id=41&Itemid=155](http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=41&Itemid=155)
- Elinder CG: Does exposure to toxic metals have a role in the development of Mesoamerican Nephropathy (MeN)? In: *Mesoamerican Nephropathy: Report from the Second International Research Workshop on MeN*. Heredia, Costa Rica, Vol. Vol. 33, edited by Wegman D, Crowe J, Hogstedt C, Jakobsson K, Wesseling C, SALTRA/IRET-UNA, 2016, pp 64–70. Available at: [http://www.saltra.una.ac.cr/index.php?option=com\\_content&view=article&id=41&Itemid=155](http://www.saltra.una.ac.cr/index.php?option=com_content&view=article&id=41&Itemid=155) (Volume 33). Accessed May 8, 2020
- Wegman DH, Apelqvist J, Bottai M, Ekström U, García-Trabanilo R, Glaser J, Hogstedt C, Jakobsson K, Jarquín E, Lucas RAI, Weiss I, Wesseling C, Bodin T; Work Health and Efficiency (WE)

- Program Working Group: Intervention to diminish dehydration and kidney damage among sugarcane workers. *Scand J Work Environ Health* 44: 16–24, 2018
25. Hansson E, Glaser J, Weiss I, Ekström U, Apelqvist J, Hogstedt C, Peraza S, Lucas R, Jakobsson K, Wesseling C, Wegman DH: Workload and cross-harvest kidney injury in a Nicaraguan sugarcane worker cohort. *Occup Environ Med* 76: 818–826, 2019
  26. Glaser J, Hansson E, Weiss I, Wesseling C, Jakobsson K, Ekström U, Apelqvist J, Lucas RAI, Arias-Monge E, Peraza S, Hogstedt C, Wegman DH: Preventing kidney injury among sugarcane workers: Promising evidence from enhanced workplace interventions. *Occup Environ Med* 2020 10.1136/oemed-2020-106406
  27. Butler-Dawson J, Krisher L, Yoder H, Dally M, Sorensen C, Johnson RJ, Asensio C, Cruz A, Johnson EC, Carlton EJ, Tenney L, Asturias EJ, Newman LS: Evaluation of heat stress and cumulative incidence of acute kidney injury in sugarcane workers in Guatemala. *Int Arch Occup Environ Health* 92: 977–990, 2019
  28. Hansson E, Glaser J, Jakobsson K, Weiss I, Wesseling C, Lucas RAI, Wei JLK, Ekström U, Wijkström J, Bodin T, Johnson RJ, Wegman DH: Pathophysiological mechanisms by which heat stress potentially induces kidney inflammation and chronic kidney disease in sugarcane workers. *Nutrients* 12: E16392020, 2020
  29. Sato Y, Roncal-Jimenez CA, Andres-Hernando A, Jensen T, Tolan DR, Sanchez-Lozada LG, Newman LS, Butler-Dawson J, Sorensen C, Glaser J, Miyazaki M, Diaz HF, Ishimoto T, Kosugi T, Maruyama S, Garcia GE, Lanaspa MA, Johnson RJ: Increase of core temperature affected the progression of kidney injury by repeated heat stress exposure. *Am J Physiol Renal Physiol* 317: F1111–F1121, 2019
  30. Chapman CL, Johnson BD, Vargas NT, Hostler D, Parker MD, Schlader ZJ: Both hyperthermia and dehydration during physical work in the heat contribute to the risk of acute kidney injury. *J Appl Physiol (1985)* 128: 715–728, 2020
  31. Mansour SG, Martin TG, Obeid W, Pata RW, Myrick KM, Kukova L, Jia Y, Bjornstad P, El-Khoury JM, Parikh CR: The role of volume regulation and thermoregulation in AKI during marathon running. *Clin J Am Soc Nephrol* 14: 1297–1305, 2019

**Received:** May 11, 2020 **Accepted:** June 17, 2020

See related commentary, “Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? Commentary” and debate, “Is an Environmental Nephrotoxin the Primary Cause of CKDu (Mesoamerican Nephropathy)? PRO,” on pages 602–603 and 591–595, respectively.