ASN LEADING THE FIGHT AGAINST KIDNEY DISEASE

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Linda S. Birnbaum, PhD, DABT, ATS
Office of the Director
National Institute of Environmental Health Sciences
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Re: Comments on National Institute of Environmental Health Sciences Strategic Plan

Dear Dr. Birnbaum:

On behalf of the American Society of Nephrology (ASN) and the 13,500 physicians, scientists, and other healthcare professionals the society represents, thank you for the opportunity to provide comments on the National Institute of Environmental Health Sciences' "Strategic Planning Pillars and Crosscut Themes." ASN leads the fight against kidney disease through education, advocacy, and research, and believes NIEHS's document outlines appropriate approaches to advancing scientific understanding of toxic and environmental risks and of preventive measures to reduce the burden of environmental exposures to populations worldwide. The society supports the outlined pillars and general approaches, but suggests that NIEHS include reference to the central role of the kidney and kidney diseases in the response to environmental challenges and diseases and the role of these environmental challenges on the kidney and kidney diseases.

Under Pillar 1, the list of "some fields [that] are moving quickly and represent areas of scientific opportunity as well as environmental public health relevance" omitted any reference to the kidney and urinary system. While it is common knowledge that the normal excretory function of the kidney is critical for responses to many if not most environmental exposures, the enormity of environmental kidney disease that occurs worldwide should not be ignored. Exposure to lead and cadmium causes major damage to the kidneys and other organs, and is growing at a rapid rate worldwide. Cadmium is a potent kidney and bone toxin, and a major worldwide pollutant resulting from both industrial and agricultural sources. General exposure levels currently approach or exceed the toxic range in many populations (see Tab #1). Environmental exposures to biologics containing kidney toxins, such as aristolochic acid, which is also taken in contaminated herbal mixtures, cause severe kidney disease and are carcinogenic. ASN suggests that kidney pharmacogenomics, other systems biological approaches, and molecular analyses of renal responses to toxicities—especially by the proximal tubule—have advanced rapidly over the past decade, creating considerable scientific opportunity and environmental public health relevance.

Diabetic patients still develop nephropathy at alarming levels and diabetic nephropathy is the most prevalent cause of end-stage renal disease (see Tab #2). Emerging evidence also

suggests, apart from traditional genetic predisposition, that epigenetic processes can persist across generations to play a modulating role in the development of renal diseases such as diabetic nephropathy (see Tab #3). Clinical and experimental studies demonstrate the occurrence of a metabolic memory of prior exposure to hyperglycemia, resulting in persistently increased risk for diabetic complications, including nephropathy, long after glucose normalization. This finding suggests a potential role for epigenetic mechanisms apart from genetic predisposition in the etiology of diabetes and its complications. In addition, there is evidence that in the uremic milieu, several features such as inflammation, dyslipidaemia, hyperhomocysteinaema, oxidative stress, and vitamin and nutritional deficiencies may affect the epigenome and impact CKD patient outcome.

The NIEHS document appropriately included the growing effect of environment on metabolic disease. ASN suggests that the role of the kidney as a critical organ with relation to metabolic disease be included in this discussion. Exciting research in the field has demonstrated the early effects of the kidney to dietary challenges, especially high caloric diets and sodium intake. The recognition that even modest decline in kidney function is a major risk factor for diabetes complications, including mortality, warrants inclusion of the kidney with any discussion of the environmental impact on metabolic diseases.

Pillar 2 of the NIEHS document mentions use of systems biological approaches to the study "of the totality of a person's environmental exposures, from all sources, across the life span." ASN suggests that the kidney, where so many toxins are concentrated and gradually accumulate (e.g., heavy metals, organic acids and bases) would be an ideal organ to examine with this systems-level approach. Moreover, human tissue from kidney biopsies and urine samples provide a remarkably accurate indicator of environmental toxin levels in kidney tissue, and are readily accessible by researchers. The accuracy and accessibility of kidney biopsy and urine samples suggest that the kidney may be better suited to the study of toxic environmental exposure in humans than other organs.

Pillar 2 also specifically mentions nutritional exposures. Excessive dietary phosphorus is a well-recognized environmental toxin in patients with CKD, causing numerous pathologic responses. Recent research documents that CKD can intensify toxicity by triggering responses that increase phosphorus excretion, including stimulation of the recently discovered circulating factor FGF-23, which augments other chronic non-communicable diseases such as cardiovascular disease (see Tabs #4-6). The unraveling of the potent harmful effects of FGF-23 on the cardiovascular system has accelerated the pace of research greatly over the last three years and could help lead to more environmental answers. These advances in FGF-23 research underscore that this is a uniquely opportune moment for NIEHS to conduct further research on the effect of environmental toxins on endocrine hormones and phosphate metabolism.

Pillar 4 of the NIEHS document refers to "Health Disparities and Global Environmental Health." CKD in general, and toxic environmental kidney disease in particular, disproportionately affect specific sub-populations that are often racial/ethnic minorities or are socioeconomically disadvantaged. The extremely high incidence of CKD and the susceptibility of populations to environmental kidney hazards in many medically underserved populations worldwide has been of increasing concern within the nephrology community. The epidemic of CKD affecting sugar cane workers on the west coast of Central America provides one compelling example of this exposure and disease burden (see Tab #7-10). According to the International Consortium of Investigative Journalists' analysis of the latest World Health Organization data, the number of men dying from kidney disease in El Salvador and Nicaragua in the last two decades has risen fivefold. Today, more men in Central America are dying from kidney disease than from

HIV/AIDS, diabetes, and leukemia combined.

Finally, as noted in the previous two paragraphs, CKD is a common chronic non-communicable disease. At present, CKD is increasing at phenomenal rates worldwide in part due to toxic exposures. More than 26 million, or 1 in 9, Americans have CKD. Most are not aware they have this disorder because it has few early warning signs. Kidney disease is the 8th leading cause of death in the U.S. Importantly, CKD interacts with environmental exposures to amplify other disease processes, such as the development of cardiovascular disease (see Tab #11). ASN therefore recommends the NIEHS follow the example of the United Nations, which this year recognized CKD as one of the most important worldwide chronic non-communicable diseases, by adding CKD in the topical statement included in "Visionary Idea #35" about the importance of these chronic diseases in environmental health.

Once again, the ASN thanks the NIEHS for soliciting comments regarding its comprehensive document outlining the themes and pillars for the institute's research emphases. We strongly believe that active consideration of toxic and environmental kidney diseases and the importance of CKD in response to toxic and environmental challenges will move the field forward at an accelerated pace. Thank you for your consideration of these suggestions. Please contact ASN Manager of Policy and Government Affairs Rachel Shaffer at (202) 640-4659 with any questions.

Sincerely,

Ronald J. Falk, MD, FASN
President