Reviewer's report

Title: Low level exposure to cadmium increases the risk of chronic kidney disease: analysis of the NHANES 1999-2006

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Reviewer: John W Kusek

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Chronic kidney disease (CKD) is a major public health problem in many industrialized countries. The search for an environmental source of the increase in end-stage renal disease and earlier stages of CKD is important. As pointed out by the authors there were several strengths of their paper including the use of a population-based sample, the U.S. National Health and Nutrition Examination Study (NHANES).

Major compulsory revisions:

How the sample of subjects was derived was not at all clear. After reading the paper several times it became more obvious that only those subject with blood and urinary cadmium levels were considered from the 1999-2006 NHANES sample. This reviewer was perplexed by the small sample size given that the NHANES sample over that time period was about three times larger. The fact that only a subsample of the NHANES was used only appears in the first paragraph of the Discussion. The authors need to indicate why the sample size was much reduced and what effect, if any, this has on their study.

The authors indicatei that urinary cadmium is a better indicator of chronic exposure to this heavy metal. However, they report that both the risk of CKD defined by a estimated GFR <60 and albuminuria are increased based on blood cadmium measurement whereas only increased blood cadmium levels showed an association for both CKD and albuminuria but not urinary cadmium (the risk was increased only for albuminuria). The authors need to further explore the relationship between blood and urinary cadmium and to indicate why urinary cadmium levels were not significantly associated with risk of CKD.

The authors make much of the importance of cigarette smoke as a source of cadmium and suggest that this exposure may be responsible, at least in part, for the epidemic of CKD observed in the U.S. The authors need to consider the increase in CKD in light of declining rates of cigarette smoking in the U.S.

The joint effect of elevated blood and urinary cadmium was not explored.

The relevance of the ROC curves was not considered in the Discussion.

Perhaps the most important shortcoming of this paper is that much of the information (at least half of the content of the manuscript) was previously
published by Navas-Acien. In that paper a much larger sample size was used. The authors need to make a compelling case that the added information on urinary cadmium justifies a separate manuscript.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.