Reviewer's report

Title: Metabolic Profiling Detects Systemic Effects of Environmental and Lifestyle Exposure to Cadmium in a Human Population.

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Reviewer: Martyn Smith

Reviewer's report:

This is a well-written paper describing the metabolic profiling of a cadmium-exposed human population. The authors report that 6 urinary metabolites, related to mitochondrial or 1-carbon metabolism were associated with cadmium exposure. In particular, citrate levels retained a significant correlation to urinary cadmium and smoking status after controlling for age, sex and renal dysfunction. Oxidative stress (as determined by urinary 8-oxo-2'-deoxyguanosine levels) was elevated in individuals with high cadmium exposure, supporting the hypothesis that heavy metal accumulation was causing mitochondrial dysfunction. These are interesting findings, albeit in a relatively small molecular epidemiology study that contains many individuals who have Cd exposures and urinary levels in the ‘normal’ range. While interesting to specialists in this field, the authors should place some caveats on their findings and one would be more convinced if the findings, especially about citrate and 8-oxo-dG had been replicated in a second exposed population. I would suggest a toning down of conclusions and calls for a revision to the Cadmium standard seem premature on the basis of these limited and exploratory findings. Further work is needed to confirm the findings and reach definitive conclusions about causal effects on the kidney by Cd.

1. Is the question posed by the authors new and well defined?
   Yes

2. Are the methods appropriate and well described, and are sufficient details provided to replicate the work?
   Somewhat. Some concern is raised by the use of “in-house code for automatic phasing, baseline correction, and referencing chemical shifts to the TSP resonance at # 0.” Could others replicate this?

3. Are the data sound and well controlled?
   Apparently so.

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
   I think so.

5. Are the discussion and conclusions well balanced and adequately supported
by the data?
Somewhat. Conclusions should be toned down and caveats presented.

6. Do the title and abstract accurately convey what has been found?
Yes.

7. Is the writing acceptable?
Yes

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

**Declaration of competing interests:**

I am a member of the Advisory Board of the MRC-HPA Centre for Environment and Health, Imperial College London, UK. I receive no fee for this position, only travel reimbursement. I have no other conflicts.