Reviewer's report

Title: The association between urinary kidney injury molecule 1 and urinary cadmium in elderly during long-term, low-dose cadmium exposure

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Reviewer: Antonio Mutti

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The manuscript “The association between urinary kidney injury molecule 1 and urinary cadmium in elderly during long-term, low-dose cadmium exposure” by Pennemans et al. highlights the diagnostic potential of KIM-1 in subjects exposed to a nephrotoxic metallic element (cadmium), owing to its correlation with urinary cadmium concentration in an elderly population after long-term, low dose exposure to cadmium in an area allegedly polluted by this metallic element.

The comparison among markers is only possible if ALL markers are measured relying on the most sensitive and reliable technique, which is not the case of this study, using a very sensitive sandwich ELISA for KIM-1 and much less sensitive methods for other renal markers.

Owing to its cross-sectional design, the present study has limited value to draw any statistical inference and the novel finding (very high correlation between urinary Cd and KIM-1 in the absence of any significant correlation with traditional markers of cadmium nephropathy) may be due to:

1. High cysteine content of KIM-1, suggesting a possible reverse correlation (high Cd binding capacity of excreted KIM-1) not necessarily due to nephrotoxicity;
2. Major methodological issues in the measurement of urinary markers: procedures to avoid the possible degradation of b2-microglobulin in acidic urine samples are missing (details should be given on urine collection, buffering and storage prior to analysis);
3. the statement “of the 140 urine samples that were tested for #2M-U, 118 were below the limit of detection of 0.206 mg/l” is not acceptable, because it suggests the inadequacy of the methodology to address the problem at hand. Methods to reliably measure for #2M-U in a physiological range have been developed in the late seventies – early eighties

The statement “as expected, the #2M-U levels exceeded the detection limit of 0.206 mg/l of the automated assay we used only in a few urine samples” in not acceptable. It is well known that the vast majority of reference values fall below the detection limit of the “automated assay” used by the authors, clearly unsuitable for the purpose of measuring this marker in the general population.

Nor is it acceptable the inference “the #2M-U assay does not detect any cell stress yet in case of low-level Cd intoxication and is therefore less sensitive than
KIM-1.”: whereas cadmium exposure cannot be avoided (Cd is an element of the earth crust), defining “low-level Cd intoxication” exposures leading to Cd-U below 1 mg/g creatinine is a challenging concept deserving attention, but requiring support by a more consistent body of evidence.

Minor issues

Please note that expressing urinary concentrations as a function of creatinine is neither a correction nor an adjustment (which would occur if the unit were the same, e.g. g/l, normalizing the numerical values to a fixed density, e.g. 1020), but a change of unit (the denominator being no longer the liter, but the gram of creatinine). I suggest to reword “correction, adjustment, etc.” throughout the text: “as a function of creatinine” or “normalized to the g of creatinine” are preferable expressions.

Additional points need to be clarified:

1. Urinary BUN (or urinary creatinine) is not a used and reliable biomarker for renal injury. Please, explain why it was used.
2. How was selected the sample size?
3. How were selected the participating individuals? Consecutively? They should be selected at random in the houses close to the pollution source. Please, explain.
4. The results were not controlled for time living in the area and distance to the sources of pollution. Please, explain.
5. How be sure that this level of KIM1 is not associated with aging? The study must have a paired control group living in an area free from cadmium contamination.

Level of interest: Too insignificant to warrant publication in any journal

Quality of written English: Not suitable for publication unless extensively edited

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