Reviewer's report

Title: Risk assessment for Thai population: Benchmark dose of urinary and blood cadmium levels for renal effects by hybrid approach of inhabitants living in polluted and non-polluted areas in Thailand

Version: 1  Date: 21 March 2014

Reviewer: Brent D. Kerger

Reviewer's report:

- Major Compulsory Revisions

1. Provide more complete documentation of the selection criteria for inclusion of subjects in the study and statistical analysis comparing the study populations for demographic factors, clinical disease states relevant to B2MG and NAG, and known risk factors for kidney disease segregated by age, existing kidney disease (kidney stones), smoking, and other confounding factors. Discuss what risk factors influence relevant kidney diseases in the general Thai population and how the prevalence of risk factors or kidney disease in the study populations compares internally (i.e., polluted vs. non-polluted) and externally (i.e., background prevalence information from the Thai population).

2. Authors need to provide a more complete description of the hybrid approach to BMDL calculations, discuss the key factors that affect uncertainty of the BMDL estimates in this population, and provide caveats regarding those uncertainties and specific confounding influences.

3. Consider the confounding influence of high kidney stone prevalence on the BMDL determination, and recalculate BMDL after excluding these individuals. If there is a basis for asserting the Cd causes or worsens kidney stone disease, provide discussion and references.

4. The small size of the control (non-polluted area) population needs to be acknowledged as a serious limitation, and parallel analyses of BMDL should be applied to them in order to examine sensitivity and uncertainty in the reported findings for the polluted area population. Also, potential selection bias must be acknowledged in that the 2007 health survey “targeted for residents suspected to have increased urinary Cd.” More background information and analysis of possible selection bias issues is needed.

5. The conclusion that “nearly half of residents aged more than 40 years old in Mae Sot, Thailand are suspected to be at risk of adverse renal effects induced by Cd” is not well supported because the methodology has not properly addressed confounding and uncertainties as noted in other comments.
6. Validity of the Discussion comparisons of current study findings to other study populations is unclear because there is insufficient information provided regarding key points of comparability, e.g., magnitude and distribution of Cd contamination and prevalence of confounding exposures (e.g., smoking) and known kidney disease risk factors (e.g., personal or family history of kidney disease).

- Minor Essential Revisions

1. Additional background on the form(s) and specific sources of Cd contamination in the contaminated areas should be provided. Specify what is known, i.e., is it primarily related to Cd stearate factories or other sources, and if the exposures are known to be primarily through food consumption versus air pollution, water pollution, or occupational exposures. Provide more information on the distribution of Cd exposures in the suspected contamination routes (e.g., rice Cd concentration and frequency distribution beyond listing percentages above a certain limit). Basis for recommended Cd limits should be explained.

2. Basis for definitions of “prevalence of dysfunction” for B2MG and NAG should be specified.

3. The Introduction text was repeated twice in the manuscript version downloaded.

4. Method for creatinine measurement in urine was not specified in the methods.

5. Authors need to better explain the scientific basis and references supporting “The BMR was defined as 5% additional risk.”

6. The methods for “profile likelihood method” should be briefly explained in the manuscript.

7. Throughout the manuscript, BMDL values are stated to be lower than geometric mean values in the polluted area, but this is not uniformly true. Restate to qualify appropriately.

8. Statement on page 15 that “blood Cd was of little relevance to the Cd concentration in urine” appears to not make sense given the reported close correlation. Please clarify what you mean.

9. Please further explain basis for hybrid BMDL approach not having an important influence from reference population results for urinary markers (p. 15).

10. Please explain statement on p. 15-16 that “reliability of BMDL in the present study was increased considerably.”

- Discretionary Revisions

None
**Level of interest:** An article of importance in its field

**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.