Review of: "Population estimates of biomarkers of exposure to carbon monoxide, nicotine, and NNK in smokers and non-smokers"

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Potential competing interests: The author(s) declared that no potential competing interests exist.

In this study, the authors explore the significance of the application of biomarkers of exposure to assess potentially reduced risk tobacco products (PRRPs) in smokers, including carbon monoxide (carboxyhemoglobin - COHb), nicotine (Nicotine Equivalents - NEQ), and nicotine-derived nitrosamine ketone (NNK; total urinary 4-[methylnitrosamino]-1-[3-pyridyl]-1-butanol [NNAL] - NNAL). Based on pooled weighted average from published literature, these data were extracted from databases , such as PubMed®, a total of 53 out of 217 scientific articles (from 2008 through 2020) were eventually included in the study.

The authors concluded that smokers had significantly higher levels of NNAL, COHb, and NEQ when compared to those of non-smokers and that there is a need to establish population level estimates for these biomarkers to determine changes in exposure for smokers switching to non-combustible products or PRRPs. The idea about the levels of NNAL, COHb, and NEQ in the smokers vs non-smokers as markers to reflect the body burden of nicotine-related risk is very interesting. In particular, the significance of the disparity of these biomarkers (especially for specific biomarkers NNAL and NEQ) in smokers before and after switching to non-combustible products is of great concern.

My comments are as follow:
It is considered that the methodology used in this study are well established (meta-analysis) and the interpretation of the findings by the authors are appropriately addressed. However, some of the exclusion criteria are not clearly stated and the respective rationale is not obvious. For example, only total urinary NNAL (sum of NNAL and NNAL-glucuronide), reported as geometric means, were included in the analysis whereas free NNAL data or total NNAL reported as the arithmetic mean was captured in the evidence table but was not included in the statistical analysis. The reviewer thinks that in order to prove their hypothesis, the authors should provide a rationale regarding the use of such an condition as an exclusion criteria.