Reviewer's report

Title: Maternal characteristics associated with the dietary intake of nitrates, nitrites, and nitrosamines in U.S. women of child-bearing age

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Reviewer: Mary H. Ward

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This is an interesting article that describes maternal characteristics associated with consumption of N-nitroso compound (NOC) precursors (nitrate and nitrite) and nitrosamines. NOC are potent carcinogens and cause congenital malformations in animal studies and there have been few recent articles on consumption levels and factors associated with intake. The topic should be of interest to exposure scientists and epidemiologists.

Major compulsory revisions:

1. Background information about the database should be provided in order for the reader to be able to better interpret the intake patterns presented. The authors should describe the general approach to the development of the database perhaps including some supplementary tables with levels in foods (optional). Additional information about estimation of nitrosamine concentrations in the foods is needed especially since this was not provided in the database manuscript. After reviewing the database paper, it was not clear if individual nitrosamines concentrations from the published literature were summed or if one nitrosamine was used as an indicator of exposure. Most studies measured N-nitrosodimethylamine (NDMA) but some studies measured multiple nitrosamines. How were these data combined to come up with nitrosamine values for each food item?

2. Tables 1 through 4 present intake quartiles of nitrate, nitrite, total nitrite (5% of dietary nitrate intake plus nitrite intake), and nitrosamines by a priori factors of interest to adverse reproductive epidemiology studies including race/ethnicity, age at conception, education, income, pre-pregnancy BMI, folate intake and multivitamin use. These tables are not adjusted for caloric intake, which would be expected to be correlated with intake. Tables 5-8 show crude and adjusted odds ratios (the latter controlling for calories and other factors) and there is often a re-ranking of the factors associated with intake compared with the earlier tables. It is not clear how much of the confounding was due to caloric intake; however, BMI and caloric intake vary by racial and ethnic groups and it would not be surprising if nitrate or nitrite intake may be a function of racial/ethnic variation in these factors. Instead of Tables 1-4, the distribution of intakes by race/ethnicity in Table 9 could be presented standardized by total calorie intake. One approach would be to use the nutrient density method, which provides meaningful units of intake in which nitrate, nitrite, and nitrosamine intake are standardized by dividing...
by total calories (presented in units of mg of intake per 1000 calories).

3. Additional information about the major food contributors to intake would help to further clarify the reasons for some of the different intake patterns that were observed across racial/ethnic groups in this study population. Animal and plant sources of nitrite should be separated because animal sources may be more important for formation of NOC because they also contain the necessary amine and amide precursors. Indeed, for some reproductive outcomes and specific cancers, animal and/or processed meat-derived nitrite shows a stronger association with risk than plant-derived nitrite. To that end, it would be particularly helpful if the authors separated meat and bean products and evaluated processed meat intakes separately from total meat or fresh meats when describing food group contributors to intake. Additional information about the top 3 to 5 individual food contributors to nitrate, nitrite, and nitrosamines intake by race/ethnicity would also be informative.

4. Dietary nitrate has shown qualitatively different associations with risk in epidemiologic studies than drinking water nitrate or dietary nitrite presumably because vegetables are the major source of intake. Some, but not all, vegetables also contain high levels of vitamin C and other antioxidants that inhibit the in vivo formation of NOC. This should be discussed especially in conjunction with the rationale for summing nitrite derived from dietary nitrate and nitrite derived from processed meats and other foods.

5. According to the database paper, there were fairly high nitrite and nitrosamine levels in the “beef, pork, and lamb”, liver, and fish line items. These high values may have been due to the equal weights that were assigned for the individual food values that comprised these line items. Assigning equal weights to each type of these foods included in the database may overestimate intake for certain line items. For example, consumption varies greatly across types of fish -- fresh fish is eaten much more commonly than smoked and pickled fish by the U.S. population. Weighting intake equally across types of fish overestimates nitrite and nitrosamine intake from fish since values are high in smoked and pickled fish but low in fresh fish. Please comment on the approach you used versus using weights based on sex- and age-specific USDA consumption data. How might your weighting approach have affected the dietary patterns you observed?

Discretionary Revisions

1. It was not clear why logistic regression was chosen for the analysis presented in Tables 5-8 instead of linear regression. Consider using linear regression models that include all factors of interest as independent variables in relation to continuous mg/day intakes of nitrate, nitrite, and nitrosamines as this would evaluate factors associated with intake across the complete range of intakes in the study population (compared with logistic models that compare high versus low intake quartiles). It would be useful to present parameter estimates for all variables that are significantly associated with one or more intakes of nitrate, nitrite, and nitrosamine so the reader can compare the magnitude of the parameter estimates for the various intakes (versus only presenting significant
variables for each type of intake).

2. The authors could comment on the fact that the highest dietary nitrate intake quartile captures the healthiest members of the population, who are high consumers of vegetables and who also tend to have higher income and folate intake.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.