Author’s response to reviews

Title: A review of the experimental evidence on the toxicokinetics of carbon monoxide: The potential role of pathophysiology among susceptible groups

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Version: 1 Date: 25 Dec 2017

Author’s response to reviews:

We thank the reviewers for their valuable comments, which we have attempted to address in the responses below. We would also like to draw the editor’s attention to our revised manuscript title. We believe that the revised title more accurately represents our review.

Original title: A review of experimental evidence on carbon monoxide and health: Does pathophysiology increase susceptibility in persons other than those with cardiovascular disease?

Revised title: A review of the experimental evidence on the toxicokinetics of carbon monoxide: The potential role of pathophysiology among susceptible groups

Reviewer 1

1. “…However, only three people died within a month after the incident and we cannot exclude that stress played the main role to increase the risk for the fatal outcome. This should be discussed in the text and if other information is available about the medical history of the surviving residents, this should be included.”

Response: While it is true that CO cannot be definitively linked as the cause of the three deaths, CO exposure was listed as a contributing factor on their death certificates. We have tried to draw attention to the fact that the three deaths occurred among elderly residents, each of whom had pre-existing morbidities, and that CO was a contributing factor: “All three were elderly, with pre-existing co-morbidities, and CO was listed as a contributing factor in each death” (page 5, second paragraph). We have additionally shortened the description of the case study to present only the most relevant information as background to our review. Unfortunately, no other
information beyond what was included in the manuscript is available for the three deaths or surviving residents.

2. Do the authors have any information on the duration of the observed effects at much lower CO-Hb levels, such those reported in Table 2, which can give evidence for an increased risk for the progression of pre-existing pathologies or for the onset of not cardiovascular diseases?

Response: The duration of the effects were not reported in the studies included in our review. We have made the following addition to our description of the studies, to clarify this point: “Additionally, the focus of the studies was on observation of the effects of target COHb levels, and no studies reported the duration of effects” (page 10, second paragraph).

3. Is the relationship between CO exposure, CO-Hb levels and adverse effects always linear?

Response: The current understanding is that the relationship between CO and COHb is non-linear, which is reflected in most models estimating this relationship, including the Coburn-Forster-Kane model cited in our paper. To clarify this point, we have added the term “non-linear” when first describing this model: “Both sets of guidelines also used the Coburn-Forster-Kane (CFK) equation to model CO-COHb relationships. This non-linear equation uses physiological parameters that influence to CO uptake and elimination and COHb formation, such as the diffusing capacity of the lungs, alveolar ventilation rate, blood volume, and partial pressure of O2 in the pulmonary capillaries [1, 11, 12]” (page 6, first paragraph).

The objective of the studies investigating COHb-outcome relationships was to examine the effects of specific COHb levels on the earliest occurrence of outcomes of interest. None of these studies investigated dose-response relationships.

4. Furthermore, if adverse effects are observed even at 2% CO-Hb level, which is the limit to derive guidelines, we should be concerned about minimal increase of CO-Hb levels in healthy population, and even more in sensitive groups of healthy population, such as children and unborn children, due to passive smoking. The authors may consider to discuss the impact of their study on the regulation of passive exposures.

Response: We agree that additional groups may be susceptible to CO, including pregnant women and children, and that smoking, both active and passive, plays an important role in CO-COHb-outcome relationships; however, we believe that a discussion of both is outside the scope of our paper. Our review focusses on the toxicokinetiscs of CO based on physiologic deficits likely
present among groups residing in long term care facilities. We also noted that our search strategy excluded impacts of smoking, both active and passive, on CO-COHb-outcome relationships.

5. The authors may consider to include the information about CO concentrations from different guidelines and recommendation in a Table.

Response: We have cited both the World Health Organization and Health Canada indoor air guidelines for CO, primarily to illustrate the limited toxicokinetic evidence on which current indoor air guidelines are based. Since the focus of our paper is on understanding potential effects of physiological deficits on susceptibility, we feel that a comparative review of indoor air guidelines for CO is outside the scope of this paper.

6. Table 2 is not very clear. The authors should find a different representation of the reported information, maybe splitting the data in two tables (healthy subjects/not-healthy subjects)

Response: We thank the reviewer for this feedback. We have now included an additional row in the table to divide data from studies of “healthy” subjects versus those of subjects from our susceptible groups of interest.

Reviewer 2

1. I would suggest that the case history is superfluous - it raised the clinical question that motivated the authors to review the literature but the details of case series do not add to the paper. It might be useful as a separate paper to highlight the limitations of COHb as a biomarker.

Response: Although we think that introducing the case example is important as it explains our motivation for the review, we have substantially reduced the description of the case study and have attempted to provide only the most relevant details for this paper.

2. Page 7: the authors report that people with COPD have reduced elimination of CO. They also have increased endogenous CO production due to secondary polycythemia and increased exposure from smoking.

Response: We thank the reviewer for this comment. We have now included the following statement: “Additionally, persons with COPD may have secondary polycythemia [15], which can increase endogenous CO production” (page 7, second paragraph).
3. Page 8: why did the authors not search Embase? It is supposed to include more toxicology and non-American articles than Medline. Also why did they not include Cochrane in their search strategy?

Response: We agree with the reviewer that it is important to have an extensive search strategy to capture all relevant articles. Our search was conducted by an Information Specialist, who confirmed that including Embase and Cochrane in our search strategy would capture articles that largely overlap with those captured using our current search strategy. However, we have clarified the details of our search to more accurately reflect its thoroughness, and we hope this clarification adequately addresses the reviewer’s concerns: “We identified articles through EBSCOhost (to access MEDLINE, CINAHL, PsycINFO, Biomedical Reference Collection, and Academic Search Complete), Ovid (to access Elsevier Science Direct, Evidence Based Medicine, SAGE journals online, and Cochrane Database of Systematic Reviews), and Google Scholar (to access books, book chapters, older articles, and articles from journals not indexed through major database platforms)” (page 8, first paragraph).

4. Page 9: the authors state that they did not identify articles published after 2008 yet they include studies published after that date in the discussion (references 73-78)

Response: We thank the reviewer for catching this error, which has now been corrected: “Our search identified 2,394 articles, of which 54 were retained, after the removal of duplicates, implementation of inclusion/exclusion criteria, and manual review of abstracts (Figure 1). All of the studies were published between 1946 and 2016” (page 9, second paragraph).

5. Page 10 is largely devoted to a description of the limitations of the Coburn-Forster-Kane equation as a model of CO uptake. Although interesting this does not directly answer the study aims (the evidence for the effect of the specified co-morbidities on CO uptake, distribution and elimination and clinical outcome.

Response: We agree that this information is not relevant to the objective of this paper, and have therefore, removed the description of these studies (page 9, second paragraph).

6. Page 12 (1st paragraph): although it is interesting to compare the changes in baseline COHb between the different groups, the small numbers and the inability to take into account the potential for smoking to act as a confounder means that the authors should not make any conclusion about whether there is a genuine difference between the groups.
Response: We thank the reviewer for this comment. First, we would like to note that all studies included in our review were conducted among non-smoking subjects. Although we agree that differences in study design make it difficult to compare findings between the studies, we do think that comparing changes in COHb among different groups, given equivalent CO exposures, is important, particularly because little information on CO-COHb relationships is available for these different groups. However, we have attempted to better highlight the limitations of such comparisons: “Differences in study design, including the exposure scenarios investigated, small sample sizes, as well as lack of reporting of baseline COHb levels limit comparisons of findings between studies, however, some comparisons are possible” (page 12, first paragraph). We have also revised a statement in our discussion to reflect this comment: “Although findings from these studies cannot be directly compared for several reasons, including differing baseline COHb levels, the lack of subject-level data, and small sample sizes, the limited evidence does suggest that higher COHb levels may occur among some groups, likely due to underlying pathology, compared with healthy persons (or persons with CVD) at equivalent CO exposures.” (page 14, first paragraph).

7. Page 12 (last 3 lines): the authors state that the relationship between higher COHb levels and outcomes were investigated but only quote levels not any outcomes.

Response: We have removed the sentence referring to the specific COHb levels: “The relationship between COHb levels > 2% COHb and outcomes were investigated for our additional groups of interest.” (page 12, first paragraph).

8. Discussion 8. Page 14 (1st 2 lines): I do not think that the authors can justify their assertion that higher levels may be expected in some groups; as stated in comment 6 above, the evidence is not robust enough

Response: We agree with the reviewer that given the limited evidence, we cannot make definitive statements that some groups will have higher COHb levels than others, given equivalent exposures. However, we do feel that it is important to note the potential for differences in resulting COHb levels, with reference to the limited evidence. We have attempted to highlight the limitations of making such comparisons (see response to comment 6).