Reviewer's report

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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Reviewer: Annamaria Colacci

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The manuscript "A review of experimental evidence on carbon monoxide and health: Does pathophysiology increase susceptibility in persons other than those with cardiovascular disease?" by Barn and colleagues explores possible relationships between physiological deficit and uptake of carbon monoxide.

The authors performed a first literature search in January 2012, which was updated in March 2017 and found that only few studies looked at the relationship between carbon monoxide exposure and percentage of carboxyhemoglobin in the blood of subjects suffering from pre-existing pathologies, such as chronic obstructive pulmonary disease, anemia, cerebrovascular disease, or of aged subjects.

The merit of this study is that it may be the first study of this kind, providing a first attempt at reviewing the guidelines values in consideration of different susceptibilities to CO exposures. Unfortunately, the collected information is not enough to draw any conclusion.

Major points,

1) The study stems from an incident in a long care facility, associated with three fatalities, following the exposure to carbon monoxide ranging from 23 and 63 ppm. Fourteen residents were hospitalized, showing CO-Hb mean values of 14.7%. Three residents, of age 89, 94 and 98 died immediately after the evacuation (one 89-year old resident) or within one month after. All three subjects suffered from pre-existing morbidities. It was possible to measure CO-Hb levels only in two of the three subjects, showing values of 15% and 16%. Even if the time at which the CO-Hb values were measured in these subjects is not known, these values fall in the measured average for all the other hospitalized evacuees. They were all resident in a long-care facility and supposedly being of old age and with possible pre-existing co-morbidities. 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.
2) Smoking is considered to increase the CO-Hb values up to 15% in heavy smokers (1-2% in non-smokers and as the consequence of passive smoking). An experimental study showed a similar increase from 0.3% CO-Hb (controls) to 14.7% CO-Hb (exposed), in female rats exposed to 200 ppm CO, 20h/day (see Sørhaug et al, 2006). These values are very similar to those registered for the hospitalized evacuees. Exposed animals developed myocardial hypertrophy in 78 weeks (a couple of animals developed the disease after 2 weeks), but no other pathologies were observed. These data give rise to a couple of questions. 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? Is the relationship between CO exposure, CO-Hb levels and adverse effects always linear? 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.

Minor points.

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

2) 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)

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