

Preliminary Comments on the ISA from Dr. Michael Kleinman

Comments on Chapter 4 – Dosimetry and Modes of Action for Oxides of Nitrogen

Chapter 4 is revised to address the CASAC Panel's advice to improve characterization of the NO₂ transport within the respiratory tract, existing dosimetric models, as well as mode of action for specific health outcome groups such as asthma exacerbation.

1. The dosimetry section (Section 4.2) expands on the description of the epithelial lining fluid in the tracheobronchial and alveolar regions. Further, the deficiencies and uncertainties associated with the lack of a validated NO₂ dosimetry model are more explicitly described. Please comment on the adequacy and clarity of these expanded discussions. To what extent does Section 4.2 address the reactive nature of NO₂ and its ability to pass beyond the epithelial lining fluid?

The revised chapter provides a more thorough review of the basis of the model and identifies the alveolar region as the target zone in which the ELF is sufficiently thin that NO₂ and reaction/metabolic products can reach and interact with underlying tissue. It is noted that there are endogenous as well as exogenous sources for NO_x and metabolites and that the concentrations of each of these are similar for many ambient situations. Table 4.1 clearly shows differences between human bronchoalveolar penetration and rat bronchoalveolar penetration. It would be helpful to include the ELF thickness in the regions shown so that the table would make it clearer that penetration through the ELF is region dependent. The bronchi and bronchioles are ciliated. The cilia are important components of the clearance process in the lung. Even though penetration to basal tissue is unlikely in the bronchial airways, the cilia may be affected and this can change rates of clearance. Reduced nasal mucocilliary clearance has been reported to be induced proportional to NO₂ exposure in urban motorcyclists[1]. The relationship of impaired clearance to increased susceptibility to respiratory system illnesses could be discussed and included in the mode of action discussion. While the evidence is still sketchy, there is an association between increased respiratory system infections and NO₂ exposures [2, 3]. There is also evidence of a relationship between increased exposure to NO₂ and ear infections [2].

2. Section 4.3 discusses mode of action for specific outcome groups and also includes new figures that describe what scientific information is available on the key events and endpoints that make up the pathophysiological changes that lead to particular health effects. What are the Panel's views on the effectiveness of the organization around the outcomes of interest?

The figures provide a useful summary of concepts. The figure captions could be phrased more specifically to highlight the key areas being discussed.

3. To what extent do the new figures facilitate integration with the health effects evidence in Chapters 5 and 6?

They provide a useful structure for the discussion. It might be useful to somehow recapitulate these figures in Table 5.1 to provide a framework that helps focus the synthesis of information.

Specific Comments:

4-34 L 4 It could be noted that the diminished response seen after repeated NO₂ exposures is consistent with O₃.

4-37 L 9 The comments on eosinophilic inflammation is linked to airway hyperreactivity later in the document, but could be mentioned here.

4-49 L 34 Alveolar bronchiolization due to NO₂ exposure is consistent with what has been reported for O₃. Perhaps this suggests similarities in effects of oxidant gases in general.

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1. Brant TC, Yoshida CT, Carvalho Tde S, Nicola ML, Martins JA, Braga LM, Oliveira RC, Leyton V, Andre CS, Saldiva PH *et al*: **Mucociliary clearance, airway inflammation and nasal symptoms in urban motorcyclists**. *Clinics (Sao Paulo)* 2014, **69**(12):867-870.
2. MacIntyre EA, Gehring U, Molter A, Fuertes E, Klumper C, Kramer U, Quass U, Hoffmann B, Gascon M, Brunekreef B *et al*: **Air pollution and respiratory infections during early childhood: an analysis of 10 European birth cohorts within the ESCAPE Project**. *Environmental Health Perspectives* 2014, **122**(1):107-113.
3. Aguilera I, Pedersen M, Garcia-Esteban R, Ballester F, Basterrechea M, Esplugues A, Fernandez-Somoano A, Lertxundi A, Tardon A, Sunyer J: **Early-life exposure to outdoor air pollution and respiratory health, ear infections, and eczema in infants from the INMA study**. *Environmental Health Perspectives* 2013, **121**(3):387-392.