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Dear Mr Mattes,

Re: Response to Professor Priestly's review on the report *Draft Literature Review and Risk Characterisation of Nitrogen Dioxide – Long and Heavily Trafficked Road Tunnels*- dated 23 February 2018

Thank you for providing enRiskS with the Priestly Toxicology Consulting Peer Review, dated 3 April 2018, of our report *Literature Review and Risk Characterisation of Nitrogen Dioxide – Long and Heavily Trafficked Road Tunnels*. We welcome Professor Priestly's feedback and have endeavoured to address this feedback. EnRiskS have identified three issues raised by Professor Priestly, which we address below.

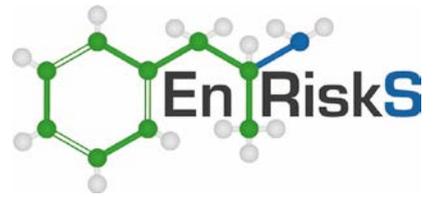
Criteria of clinical relevance

Prof. Priestly Comment: However, it might have been useful to flag, where appropriate, whether lung function criteria used in individual original studies may have differed from the criteria determined to be most appropriate for the EnRiskS report, and how this may have been handled by EnRiskS in compiling their tabulated analyses.

EnRiskS Response: Section 2.6 of the report summarises the clinical criteria used to assess clinical relevance in the report. These clinical criteria are based on standard respiratory clinical tests. In most instances these standard respiratory clinical tests were used in the individual studies reviewed. **Tables 3.1 – 3.4** provide the test outcome in the individual studies and the criterion they were assessed against, for studies found to be statistically significant. Where studies were not compared against any criterion (See Tables 3.1-3.4 - Bylin 1985, Mohsenin 1987, Larsson 2010) this was due to a lack of information provided in the study paper.

Broader search term

Prof. Priestly Comment: Using a broader search term (e.g. nitrogen dioxide, NO₂, air, health effects) would have captured a broader range of studies, including epidemiological studies of road traffic-related air pollution and health where NO₂ exposure may not have been the main target. Indeed, a brief search using this broader term does capture a range of such studies, some of which that have been more recently published are listed in the Appendix A to this peer review. I do not think these more recent studies detract from anything raised in the EnRiskS report, nor do they really contribute anything more substantive to the analysis of NO₂ dose response relationships.



EnRiskS Response: The search terms were based on previous work undertaken by Jalaludin et al¹ and the scope of the literature review as presented in **Section 1.2** of the enRiskS review. This approach identified 38 more studies than the previous review by Jalaludin et al. Professor Priestly is correct in his assumption that the search terms were devised to focus the literature survey on experimental studies, where the short term (1 hour) dose-response relationships could be more specifically refined. As noted in **Sections 3.5 – 3.7** of the enRiskS review experimental studies have provided the foundation of short term (1 hour) NO₂ guidelines.

There is a plethora of studies examining air pollution and health effects, and therefore the search terms were devised to best identify those studies that could provide evidence regarding short term health impacts, in line with likely in-tunnel NO₂ exposures of up to 1 hour. It is noted that most observational epidemiological studies use exposure times of 24 hours or greater including all but one paper identified by Professor Priestly in Appendix A of his report. This paper (Shinharay et al 2018), has been analysed further in **Attachment A** of this letter. Nonetheless our report has not ignored observational studies. **Section 4** addresses observational studies, including **Section 4.5** which specifically reviews the limitations of observational studies in setting a 1-hour NO₂ guideline. Finally, we note Professor Priestly's comment that he does not *think these more recent studies* (identified from a broader search term) *detract from anything raised in the EnRiskS report, nor do they really contribute anything more substantive to the analysis of NO₂ dose response relationships*. This view is reinforced by our assessment of Shinharay et al paper in **Attachment A**.

NO₂ conversions

Prof. Priestly Comment:it might have been helpful if the Report could indicate, via a footnote, the equation used to make the conversion calculations ($\mu\text{g}/\text{m}^3$ to ppm) and where this was done from the original data.

EnRiskS Response: Agreed. The tables in Appendix B - D have been updated to reflect this.

We trust this has addressed Professor Priestly's comments. If you require any additional information or wish to discuss any aspect of the report or our response further, please do not hesitate to contact us.

Yours sincerely,

Dr Jackie Wright (Fellow ACTRA)
Principal/Director
Environmental Risk Sciences Pty Ltd

Dr Adam Capon (Registrant ACTRA)
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Attachment A – Review of Shinharay et al (2018)

¹ A review of the health effects of NO₂ prepared by the Woolcock Institute of Medical Research, Centre for Air quality and health Research and evaluation (CAR) by Professor Bin Jalaludin, dated 22 April 2015



Attachment A

The paper by Sinharay et al 2018 examines the impact of walking along a busy road and walking in a park. The researchers take three groups of elderly people (healthy, those with chronic obstructive pulmonary disease (COPD) and those with ischaemic heart disease (IHD)) and randomly assigned them to walk either along a busy road or in a park for two hours. The people then repeat the walk in the other environment (either the road or park) 3 to 8 weeks later. NO₂ concentrations were measured, however as the paper is seeking to determine the impact of walking along a busy road and walking in a park and not walking along a busy road versus walking in a park, it does not report the road and park NO₂ concentrations in terms of differing exposure between the busy road versus the park, with comparison to a linked difference in FEV₁ and FVC measurements between the two exposures. It does however present graphically the FEV₁ and FVC difference between the road and park exposures (refer to **Figure 1** – taken from Figure 4 (Sinharay et al. 2018)). Examination of **Figure 1** shows that although some time periods had statistically significant differences in FEV₁ and FVC values, at no time is the average difference in FEV₁ or FVC greater than 12% for either the Healthy, COPD or IHS cohorts, and therefore under the Criterion 1 & 3 set in the enRiskS review, would not be considered clinically relevant.

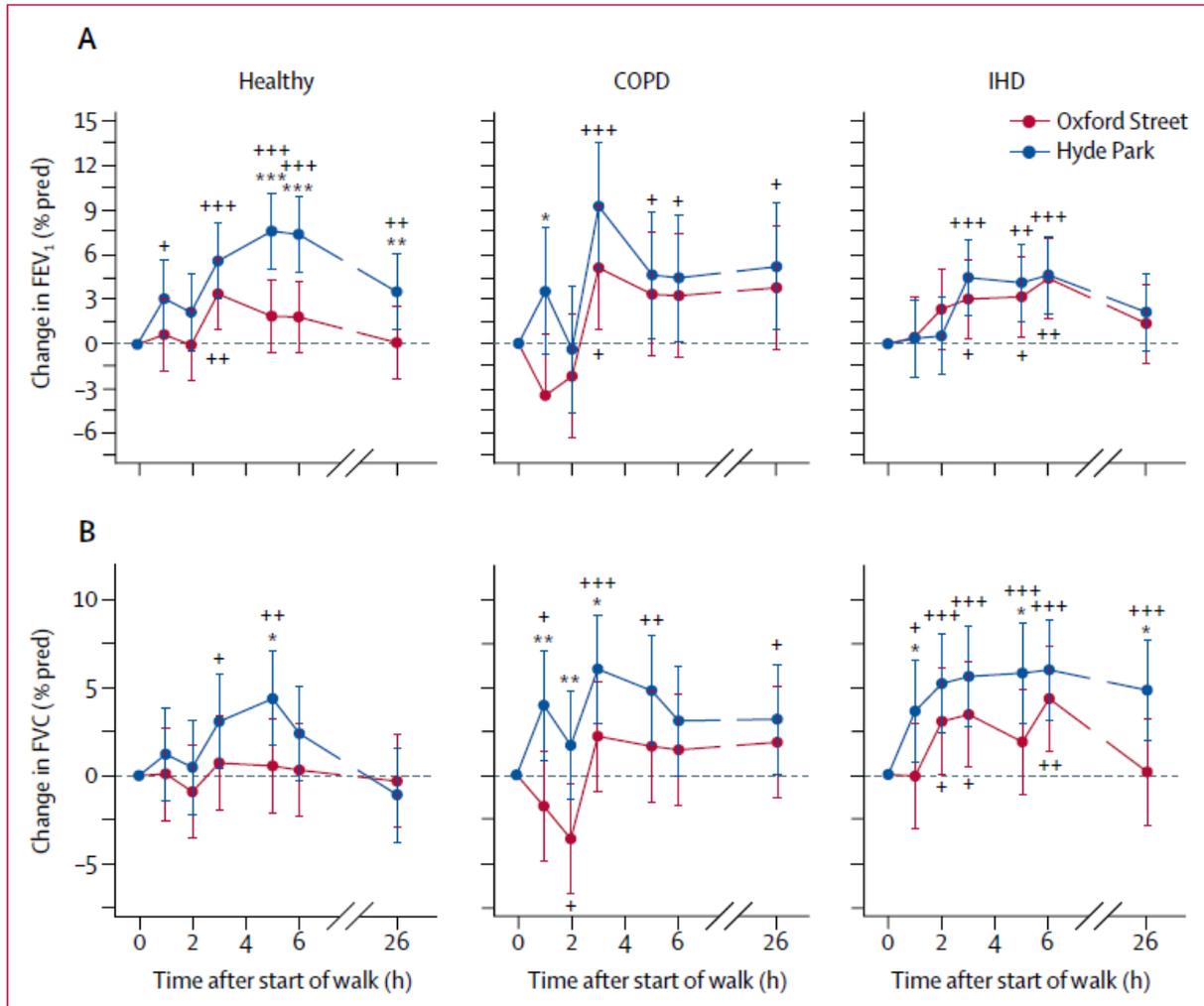


Figure 4: Change in FEV₁ % of predicted value (A), and FVC % of predicted value (B) from the baseline (time 0) and at 1 and 2 h after the start of the walk in Oxford Street or Hyde Park followed by measurements performed back in the laboratory at times indicated after the start of the walk for healthy volunteers and participants with COPD or IHD

Data are percentage changes (95% CI). COPD=chronic obstructive pulmonary disease. IHD=ischaemic heart disease. FEV₁=forced expiratory volume in the first second. FVC=forced vital capacity. *p<0.05, **p<0.01, ***p<0.001, comparing Oxford Street with Hyde Park. +p<0.05, ++p<0.01, +++p<0.001, compared with timepoint 0.

Figure 1: Figure 4 from Sinharay et al (2018)

Reference

Sinharay, R, Gong, J, Barratt, B, Ohman-Strickland, P, Ernst, S, Kelly, FJ, Zhang, J, Collins, P, Cullinan, P & Chung, KF 2018, 'Respiratory and cardiovascular responses to walking down a traffic-polluted road compared with walking in a traffic-free area in participants aged 60 years and older with chronic lung or heart disease and age-matched healthy controls: a randomised, crossover study', *The Lancet*, vol. 391, no. 10118, pp. 339-349.