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Peer Review: EnRiskS report on a Literature Review and Risk Characterisation of Nitrogen Dioxide in Long and Heavily Trafficked Road Tunnels

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[1] The relevant experience brought to this task by the author includes:

- Fifteen years of leadership of the Australian Centre for Human Health Risk Assessment at Monash University (part time since 2009)
- Experience in regulatory toxicology in former leadership appointments to the Commonwealth Department of Health in areas of toxicological assessment of agricultural & veterinary chemicals, regulation of medicines, and assessment of chemicals for poisons scheduling
- More than 45 years experience with government expert committees and panels assessing chemical toxicity and chemicals risk management, including issues of air quality assessment
- Peer-reviewed recognition as a Fellow of the Australasian College of Toxicology & Risk Assessment (ACTRA), a professional organisation that I helped to found and for which I served as its inaugural President.

The opinions set out in this report are my own, and do not reflect views of any current (Monash University) or previous employers.

The purpose of this peer review report is not to endorse any particular value for a health-based air quality Guideline Value (GV) for nitrogen dioxide (NO_2) emissions in road tunnels, but simply to comment on the draft report (dated 27 February 2018) reviewing relevant literature and prepared by consultants Environmental Risk Sciences Pty Ltd (EnRiskS). Likewise, the purpose of the EnRiskS report was not to recommend any specific GV, but to review the available literature on human health effects of NO_2 with a view to assisting the Advisory Committee on Tunnel Air Quality to determine whether established guidelines for in-tunnel air quality (currently 0.5 ppm as a rolling 15 minute average) remain appropriate.

In summary, I find the EnRiskS report to be a thorough and well-presented review of the relevant available literature up to September 2017.

Section 2 of the EnRiskS report includes a concise summary of the effects of NO_2 on the lung. It draws heavily on an authoritative US EPA 2016 report and provides a basis for understanding why effects on lung function have been the main focus for studies on both short- and long-term health effects. There is a useful diagram (copied from the 2016 US EPA Report) that outlines NO_2 mode of action pathways, the preclinical biomarkers, lung function markers and disease outcomes that are described in most of the reviewed papers. It is helpful to understand the biological responses in order to be able to differentiate between responses to acute and chronic NO_2 exposures.

There is a useful discussion of the approaches taken by different agencies (US EPA, WHO and the Australian NHMRC, TSANZ and NACA) to defining clinically relevant health effects of air pollutants. The derived criteria of lung function (set out in Section 2.6) are then used to analyse the studies reviewed later in the Report. 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.

Section 3 addresses the main topic of the EnRiskS report – a literature review outlining a quite extensive range of studies on the effects of NO_2 on lung and cardiovascular functions in humans, with a specific focus on experimental studies in humans involving controlled exposures or other epidemiological studies where dose-response relationships may be elucidated. These studies have been summarised in diagrammatic format and in well-constructed and informative tables in Appendix B.

Section 3 also contains a useful discussion of the basis used by various authorities for setting short-term and long-term GVs for NO_2, and it explains why lower GVs for NO_2 (0.1 -0.12 ppm 1h average) have been set by WHO the US EPA and in the Australian NEPM. In this context, a recent review[2] of differing national GVs for NO_2 and other air quality criteria pollutants adds substance to this analysis, and show that 1h GV have clustered around 200 $\mu g/m^3$, with some as high as 400 $\mu g/m^3$ (0.08 – 0.12 ppm). There is further discussion in Sections 4.5 and 5 of the EnRiskS report of how different policy approaches have been used in setting short-term NO_2/NOx GVs

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[2] Joss M.K. *et al* (2017). Time to harmonize national ambient air quality standards. *Internat. J. Public Hlth.* **62**: 453-462.

Section 4 is the more critical part of the EnRiskS report, since it addresses the way that experimental and other studies of NO_2 health effects have been used to establish air quality GVs. This discussion includes a detailed analysis of two key reports that have been used by various authorities (including the Advisory Committee on Tunnel Air Quality) to establish air quality GVs for road tunnels. These reports are:

- A review of the health effects of NO_2 prepared by the Woolcock Institute of Medical Research, Centre for Air quality and health Research and evaluation (CAR) by Professor Bin Jaluladin, dated 22 April 2015[3].
- An assessment of long-term health impacts of air quality with different guideline values for NOx[4] in the planned by-pass tunnel Förbifart Stockholm, prepared by Orru & Forsberg from the Umeå University, Environmental & Occupational Medicine unit (report dated 2016).

I have also reviewed these two reports and I agree with the EnRiskS analysis of them and of their utility in guiding decision-makers in setting air quality GVs for NO_2.

Another critical component of the EnRiskS report is the Section 6 discussion of how exposure times relating to tunnel traffic movements could influence the setting of NO_2 GVs. It also makes the important point that, for cars and trucks, closing windows and ventilation systems can result in NO_2 exposures substantially less than external ambient levels for short tunnel transits.

An overall summary of the outcomes of the EnRiskS report is contained in the following extract from the Executive Summary:

> *"This review examined experimental studies to determine if exposures of nitrogen dioxide at 0.5 ppm for up to 60 minutes was likely to cause a clinically relevant health effect. Seventy-eight studies were reviewed and although twelve studies examining health effects of nitrogen dioxide exposure up to 0.5 ppm for up to 60 minutes found a statistically significant result, none of these studies were determined to have a clinically relevant health effect*."

I find this to be an accurate analysis and fairly based on the reviewed literature. I note that in the majority of the short-term exposure studies (≤30 minutes; ≥30 - ≤60 minutes), airway responsiveness was the more sensitive marker of effect, and that all of the positive effect studies were conducted in asthmatic subjects. This provides for more susceptible members of the population to be protected by air quality GVs based on these types of data. Studies where the NO_2 responses were related to traffic-related air pollution (Table 3.3) generally resulted in less marked effects, or possibly effects that were more difficult to attribute solely to NO_2 exposure.

Section 3.2.3 includes a useful summary of the analysis of available meta-analyses of the experimental studies from the 2005 Jalaludin report. This discussion confirms the

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[3] The Jalaludin 2005 report, along with a review of other relevant air quality GVs, has been used to set the current NSW NO_2 air quality guideline value of 0.5 ppm

[4] There is a useful discussion of the differences between setting standards based on NO_2 and NOx, and the reasons the Swedish authorities chose to base their GVs on NOx.

view that positive effects on lung function and airway responsiveness at exposure levels below 0.5 ppm were not clinically relevant.

Some additional comments on selected elements of the Report

- It is noted that the search terms (‘nitrogen dioxide’ and ‘chamber’) used to find relevant papers in the literature review were somewhat limited, and the literature was only surveyed up to September 2017. Presumably, this was to address the focus of the literature survey on experimental studies where the dose-response relationships could be more specifically refined. Using a broader search term (e.g. nitrogen dioxide, NO_2, air, health effects) would have captured a broader range of studies, including epidemiological studies of road traffic-related air pollution and health where NO_2 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[5]. 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 NO_2 dose response relationships. It is often difficult to separate the effects of NO_2 from other constituents of ambient air pollution in such epidemiological studies, and many of the measured health impacts reported on relate to average exposures over a longer period. Moreover, the discussion in Section 3.3 recognises the limitations of extrapolating from experimental studies where airborne NO_2 was the sole challenge, to the more complex real-world situation where multiple pollutants from traffic exhausts would be the source for possible adverse health effects.

- It is useful that Figures B1 – B3 and Tables B1 – B3 summarise the reviewed studies in groups relating to the duration of exposure (≤30 minutes; ≥30 - ≤60 minutes and >60 minutes). It is also useful that the diagrammatic representation allows for comparison with the current 0.5 ppm air quality GV, and that the statistical significance is colour-coded. The Tables have been ordered from the lowest to highest NO2 exposures, to align with the Figures, and they contain a wealth of relevant information on single vs repeated exposures, subject age and smoking history, influence of exercise, and the specific outcomes measured. Altogether, a commendable way of representing a large amount of data.

- It is also useful, for comparison purposes, that the exposure data for NO_2 has been expressed in ppm throughout the Figures and Tables, while some of the original papers would have expressed it in $\mu g/m^3$. I have done only minimal checks to ensure the accuracy of the exposure concentration conversion, but it might have been helpful if the Report could indicate, via a footnote, the equation used to make the conversion calculations and where this was done from the original data.

- I share the author’s scepticism over the application of Haber’s Rule to convert the exposure times in experimental studies on air pollution (Section 4.4.2) despite its endorsement by Australian authorities, including NHMRC and enHealth.

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[5] The list of some more recent papers found using a broader search term is appended. Most of these are epidemiological studies of more generalized effects of air pollutants, so may be of more limited utility in informing the short-term air quality guideline that is the subject of the EnRiskS report.

However, while it remains one of the few tools that can be used for such time conversions, I suggest that more weight be given to studies where the exposure times are more relevant to the averaging time for guideline setting, with less weight given to those where Haber's Rule has been applied. In this context, the analysis presented in Table 4.2 provides a more useful way of approaching the complex issue of interpreting time-related exposure-effect relationships, with acknowledgement of the limitations outlined in the EnRiskS report.

Appendix A: List of recent papers retrieved from PubMed using a broader search term

Bai L. *et al* (2018). Exposure to ambient ultra fine particles and nitrogen dioxide and incident hypertension and diabetes. Epidemiol. Doi 10.1097/EDE.0000000000000798 published ahead of print

Bowatte G. *et al* (2017). Traffic-related air pollution exposure over a 5-year period is associated with an increase risk of asthma and poor lung function in middle age. *Eur. Respir. J*. **50**: 1602357

Cai Y. *et al* (2018). Road traffic noise, air pollution and incident cardiovascular disease: a joint analysis of the HUNT, EPIC-Oxford and UK Biobank cohorts. *Environ. Internat*. **114**: 191-210.

Collart P. *et al* (2018). Short-term effects of nitrogen dioxide on hospital admissions for cardiovascular disease in Wallonia, Belgium. *Internat. J. Cardiol*. **255**: 231-236.

Greenberg N. *et al* (2017). Modeling long-term effects attributed to nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) exposure on asthma morbidity in a nationwide cohort in Israel. *J. Toxicol. Envir. Hlth. Part A*. **80**: 326-337.

Hanigan I.C. *et al* (2017). Blending multiple nitrogen dioxide data sources for neighborhood estimates of long-term exposure for health research. *Environ. Sci Technol***. 51**: 12473-12480.

Khreis H. *et al* (2017). Exposure to traffic-related air pollution and risk of development of childhood asthma: as systematic review and meta-analysis. *Environ. Internat*. **100**: 1-31.

Panis L.I. *et al* (2017). Short-term air pollution exposure decreases lung function: a repeated measures study in healthy adults. *Environ. Hlth*. **16**: 60.

Pedersen M. *et al* (2017). Exposure to air pollution and noise from road traffic and risk of congenital anomalies in the Danish National Birth Cohort. *Environ. Res*. **159**: 39-45.

Roswall N. *et al* (2017). Long-term residential road traffic noise and NO2 exposure in relation to risk of incident myocardial infarction – a Danish cohort study. *Environ. Res*. **156**: 80-86.

Sinhary R. *et al* (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 randomized crossover study. *Lancet* **391**: 339-249.

Su T.C. *et al* (2017). Association between long-term exposure to traffic-related air pollution and inflammatory and thrombotic markers in middle-aged adults. *Epidemiol*. **Oct 28 Suppl1**: S74-S81

Ward-Caviness C.K. *et al* (2016). Short-term NO_2 exposure is associated with long-chain fatty acids in prospective cohorts from Ausburg, Germany: results from an analysis of 138 metabolites and three exposure. *Internat. J. Epidemiol*. **45**: 1528-1538.

Wing S.E. *et al* (2017). Chronic exposure to inhaled, traffic-related nitrogen dioxide and a blunted cortisol response in adolescents. *Environ. Res*. **163**: 201-207.

Yang B-Y. *et al* (2018). Global association between ambient air pollution and blood pressure: a systematic review and meta-analysis. *Envir. Pollution* **235**: 576-588

Yoda Y. *et al* (2017). Acute effects of air pollutants on pulmonary function among students: a panel study in an isolated island. *Envir. Hlth & Preventive Med*. **22**: 33.