

Peer Review Report

Review Report on Long-term exposure to nitrogen dioxide and ozone and mortality: Update of the WHO air quality guidelines systematic review and meta-analysis

Review, Int J Public Health

Reviewer: Aaron Cohen

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EVALUATION

Q 1 Please summarize the main theme of the review.

The authors report the results of a systematic review and meta-analysis of the literature on mortality associated with long-term exposure to nitrogen dioxide and ozone extending by six years an earlier review (Huangfu and Atkinson 2020) which informed the current WHO air quality guidelines. In that time the literature has grown in size and in geographic scope, importantly now including more studies from Western Pacific (China). The authors apply in most important respects the same methods used in the earlier review, methods considered by WHO and others state-of-the-art for such reviews and results reported clearly and in detail. The authors report that there is now stronger evidence (“certainty”) regarding the effects of long-term exposure to nitrogen dioxide on mortality from all-cause and cardiovascular and respiratory disease with the exception of cerebrovascular disease, and “high certainty” for annual exposure to ozone and respiratory mortality. This updated review is timely and provides important new information on the current state of the evidence. Several areas require additional discussion.

Q 2 Please highlight the limitations and strengths.

This updated review is timely and provides important new information on the current state of the evidence. Several areas require additional discussion.

The authors conclude that the updated review “...provides the necessary input [emphasis mine]to base future burden of disease calculations in order inform related policies.” I respectfully disagree.

- Surely, these results can contribute but the authors fail to address the issue clearly stated by Huangfu and Atkinson 2020, page 23): “This review of associations between NO₂ and O₃ and mortality in epidemiological cohort studies provides evidence for the assessment of strength of associations only. It has focused on results form [sic] single pollutant models. The question of the independence of these associations from other pollutants requires careful consideration. A separate causal determination is required to proceed to quantification of health impacts.” The authors owe the reader a more thoughtful discussion of this issue. For example, do they think that cardiovascular deaths attributable to NO₂ and PM_{2.5} are additive? If not, why not? If so, what are the implications for burden estimation? The GBD Collaboration has taken what might be termed a conservative approach: NO₂ is the basis only for estimates of childhood asthma incidence based on the same issues raised by Huangfu and Atkinson and in keeping with HEI Traffic Review and USEPA. What do the authors suggest that GBD and WHO should do based on their results?

- Burden of disease calculations for air pollution do not exist, and are not used, in isolation. Both WHO and the GBD Collaboration provide countries with comparative estimates of mortality attributable to a range of major risk factors which comparisons are critical to priority setting and decision-making and require an assessment of the comparative strength of evidence among major risk factors. Since the publication of the updated WHO AQGs the GBD Collaboration has applied a Burden of Proof approach (<https://www.healthdata.org/data-tools-practices/interactive-visuals/burden-proof> ; Zheng P et al. <https://www.nature.com/articles/s41591-022-01973-2>) that grades the strength of the evidence for air pollution and other risk factors using an internally consistent approach which in which unexplained inter-study

heterogeneity plays a key role in assigning the level of strength (the more heterogeneity the weaker the evidence). At a minimum, the authors need to acknowledge these complexities and offer WHO and other readers some initial thoughts on how their assessment of heterogeneity compares to Burden of Proof.

Q 3 Please provide your detailed review report to the authors, structured in major and minor comments.

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PLEASE COMMENT

Q 4 Does the reference list cover the relevant literature adequately and in an unbiased manner?

For the most part but some additions are suggested

Q 5 Does this manuscript refer only to published data? (unpublished data is not allowed for Reviews)

Yes.

Q 6 Does the manuscript cover the issue in an objective and analytical manner

Yes.

Q 7 Was a review on the issue published in the past 12 months?

No.

Q 8 Does the review have international or global implications?

Yes

Q 9 Is the title appropriate, concise, attractive?

Yes

Q 10 Are the keywords appropriate?

Yes

Q 11 Is the English language of sufficient quality?

Yes

Q 12 Is the quality of the figures and tables satisfactory?

Yes.

QUALITY ASSESSMENT

Q 13 Quality of generalization and summary



Q 14 Significance to the field



Q 15 Interest to a general audience



Q 16 Quality of the writing



REVISION LEVEL

Q 17 Please take a decision based on your comments:

Minor revisions.

