PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data.
AUTHORS	ten Have, Pieter; van Hal, Peter; Wichers, Iris; Kooistra, Johan; Hagedoorn, Paul; Brakema, Evelyn A; Chavannes, Niels; de Heer, Pauline; Ossebaard, Hans

VERSION 1 – REVIEW

REVIEWER	Faezipour, Misagh Middle Tennessee State University, Engineering Technology This work has merit, is well written and structured. This is an interesting article about replacing MPIs with DPIs and the impact on climate in the respiratory health sector. They used a four-step analysis based on data from two national databases of two independent governmental bodies and showed the results from an environmental health benefit perspective and financial impact.
REVIEW RETURNED	03-Oct-2021

GENERAL COMMENTS	This work has merit, is well written and structured. This is an interesting article about replacing MPIs with DPIs and the impact on climate in the respiratory health sector. They used a four-step analysis based on data from two national databases of two independent governmental bodies and showed the results from an environmental health benefit perspective and financial impact. The paper is well organized and written in a logical order.

REVIEWER	Robin, Alan Johns Hopkins Medicine School of Medicine, Opthalmagy
REVIEW RETURNED	28-Dec-2021

GENERAL COMMENTS	This is an important and well written manuscript. Might I make a few suggestions? Although the direct effect of F-gasses are a significant factor, an LCA is really the way to accurately analyze the carbon footprint of MDIs and DPIs. The authors acknowledge this in their discussion, but this should be emphasized throughout the manuscript, as the F-gas effect alone may be misleading. The authors assume 100% adherence. Might they become more realistic and assume the work of Vrijens, Vincze, et al (.BMJ 2008;336;1114-1117) regarding adherence to anti-hypertensive medications reflects adherence to inhalers? If they agree, might they then recalculate their findings? The authors assume equal bioavailability and efficacy of the MDI and DPI. If the DPI is less effective, more would be needed, thus changing the calculations. From a health economics perspective, if the DPI is less effective, causing a hospitalization or other morbidity,

	the authors might also consider these type of calculations. Might the authors change the first sentence of the introduction to "...is one of the greatest ...threats...of this century, potentially inflicting...."

VERSION 1 – AUTHOR RESPONSE

	Comment	*Authors' response*
Reviewer 2	Although the direct effect of F-gasses are a significant factor, an LCA is really the way to accurately analyze the carbon footprint of MDIs and DPIs. The authors acknowledge this in their discussion, but this should be emphasized throughout the manuscript, as the F-gas effect alone may be misleading.	In the Discussion section we explain that inhalers and spacers differ from one another in material use. They also differ with regard to their development, distribution and manufacturing process. Like Wilkinson et al., as of now we lack sufficient and reliable data on the life cycle assessments of all these different brands of inhalers. But the propellant driven aerosols are most important in terms of climate impact, and we believe this imperfect analysis is a good start to tackle this pressing problem. More and better data in the future will most certainly provide additional reasons for replacement.
Reviewer 2	The authors assume 100% adherence. Might they become more realistic and assume the work of Vrijens, Vincze, et al (BMJ 2008;336;1114-1117) regarding adherence to anti-hypertensive medications reflects adherence to inhalers? If they agree, might they then recalculate their findings?	We have assumed a 100% implementation to estimate the maximum impact which can safely be achieved. We thus provide a 'ceiling' of the potential effect. In the Discussion section we explain that the correct level of implementing the proposed substitution is hard to predict, but that if someone has an idea what it actually could be in practice, the impact can easily by calculated from the provided data in the present paper. Thank you for suggesting Vrijens et al. The CO2 impact we calculate does not depend on the level

		of (patient) adherence to doctors' advice. We know exactly how many inhalers are delivered to patients by pharmacies, how much propellant is involved and how much propellant will end up in the atmosphere. Via intended use, or after long storage in a closet or after deposit at the local dump where oxidation of the canister will eventually set the propellant free to the atmosphere. We do not know if the patient uses the inhaler as intended, but it would not influence the CO2 impact.
Reviewer 2	The authors assume equal bioavailability and efficacy of the MDI and DPI. If the DPI is less effective, more would be needed, thus changing the calculations. From a health economics perspective, if the DPI is less effective, causing a hospitalization or other morbidity, the authors might also consider these type of calculations.	In the Results section we explain that differences in bioavailability between pMDIs and DPIs are corrected for by the daily defined dose (DDD).
Reviewer 2	Might the authors change the first sentence of the introduction to "...is one of the greatest ...threats...of this century, potentially inflicting...."	We believe the opening sentence *'Climate change is the greatest global health threat of our times, inflicting a range of ill health outcomes including (re-)emerging zoonoses such as Covid-19, non-communicable diseases and mental health disorders'* indicates without exaggeration the urgency of finding sustainable solutions in society in general, and health care in particular. The evidence for the health effects of the ecological crises has since then only increased

		(IPCC report, Aug 2021; Lancet Countdown report Dec 2021 et cetera.). We would therefore prefer the sentence to be kept as it is.

VERSION 2 – REVIEW

REVIEWER	Faezipour, Misagh Middle Tennessee State University, Engineering Technology
REVIEW RETURNED	05-Mar-2022

GENERAL COMMENTS	The authors have done a good work to address the comments and revise the article. No further comments.