

Thoughtful prescription of inhaled medication has the potential to reduce inhaler-related greenhouse gas emissions by 85%

Ville Vartiainen ,¹ Ashley A Woodcock,² Alex Wilkinson ,³ Christer Janson ,⁴ Unnur Björnsdóttir,⁵ Tari Haahtela,⁶ Lauri Lehtimäki⁷

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ABSTRACT

Introduction Both physicians and patients are increasingly aware of the environmental impacts of medication. The shift of treatment paradigm towards MART-treatment (Maintenance and Reliever Therapy) in asthma affects the treatment-related emissions. The carbon footprint of inhaled medication is also tied to the type of the device used. Today the most commonly used propellant-containing pressurised metered-dose inhalers (pMDIs) have a carbon footprint typically 20–40-fold higher than propellant-free dry powder inhalers (DPIs) and soft mist inhalers.

Methods We analysed the carbon footprint of inhaled medications in Europe using published life cycle analyses of marketed inhalers and comprehensive 2020 European sales data. In addition, we give an estimate on treatment-related emissions of different treatment regimens on Global Initiative for Asthma (GINA) step 2.

Results There is potential to reduce the carbon footprint of inhaled medications by 85% if DPIs are preferred over pMDIs. Emissions from pMDIs in the EU were estimated to be 4.0 megatons of carbon dioxide equivalent (MT CO₂e) and this could be reduced to 0.6 MT CO₂e if DPIs were used instead. In the treatment of moderate asthma with DPI, an as-needed combination of inhaled corticosteroid and long-acting beta-agonist in a single inhaler had a substantially lower annual carbon footprint (0.8 kg CO₂e) than the more traditional maintenance therapy with an inhaled corticosteroid alone with as-needed short-acting beta-agonist (2.9 kg CO₂e).

Discussion There has been an urgent call for healthcare to reduce its carbon footprint for appropriate patients with asthma and chronic obstructive pulmonary disease (COPD), changing to non-propellant inhalers can reduce the carbon footprint of their treatment by almost 20-fold.

INTRODUCTION

The WHO has estimated that increases in malnutrition, malaria, diarrhoea and heat stress due to climate change will cause 250 000 deaths per year between 2030 and 2050.¹ The treatment paradigm has a large effect on how and when the medication is used and is therefore, tied to the treatment-related greenhouse

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Propellant gases used in pressurised metered-dose inhaler (pMDI) devices are known to be potent greenhouse gases and pMDI are considered to have a significantly larger environmental impact compared with dry powder inhalers (DPIs).

WHAT THIS STUDY ADDS

⇒ In this work, we report the use of pMDI-based medication in 2020 and the effect of Maintenance and Reliever Therapy-treatment on treatment-related emissions. The carbon footprint of inhaler treatment can be reduced by 85% by using non-propellant inhalers without compromising the treatment.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Replacing 90% of pMDIs in Europe with DPIs or soft mist inhalers would equal to removing 1.5 million cars from the roads in terms of greenhouse gas emissions. Preferentially using greener inhalers would reduce the environmental impact of inhaler treatment without compromising treatment.

gas emissions of asthma. During the past few years, the international treatment guidelines for asthma have shifted from regular maintenance and as-needed reliever therapy towards Maintenance and Reliever Therapy (MART). Today the most commonly used propellant-containing pressurised metered-dose inhalers (pMDI) have a 20–40-fold higher carbon footprint compared with propellant-free dry powder inhalers (DPI).² Selection of inhalers in the treatment of respiratory disease is, therefore, a prime example of how healthcare professionals can directly reduce emissions of greenhouse gases.

The health benefits to the patient must be the physician's first priority. There are several safe and effective inhaled medications for asthma and COPD, which are available in a range of different inhaler devices. Most



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For numbered affiliations see end of article.

Correspondence to

Dr Ville Vartiainen;
ville.vartiainen@helsinki.fi

Table 1 Carbon footprint per dose of each inhaler with available LCA and MCTOC estimate of device type-specific average footprints

Inhaler	Type	Carbon footprint per dose (gCO ₂ e)
DPI (general MCTOC estimate) ²	DPI	<20
pMDI (general MCTOC estimate) ²	pMDI	100–150
Buventol Easyhaler ²⁸	DPI	3.1
Bufomix Easyhaler ²⁸	DPI	4.0
Formoterol Easyhaler ²⁸	DPI	4.3
Budesonide Easyhaler ²⁸	DPI	3.3
Beclomethasone Easyhaler ²⁸	DPI	3.1
Salflumix Easyhaler ²⁸	DPI	9.5
Relvar Ellipta ²⁹	DPI	25.5
Seretide Diskus ²⁹	DPI	20.9
Seretide Evohaler ²⁹	pMDI	229.5
Ventolin Diskus ⁶	DPI	10
Ventolin Evohaler ⁶	pMDI	140
Spiriva Respimat ³⁰	SMI	12.9
Berodual ³⁰	pMDI	82.4
Berodual Respimat ³⁰	SMI	6.5
Atrovent ³⁰	pMDI	72.9
Clenil ²¹	pMDI	83.1
Foster ²¹	pMDI	94.4
Foster Nexthaler ²¹	DPI	7.6
Trimbow ²¹	pMDI	119.0

Inhalers from different LCAs are not directly comparable, but data are presented as it was reported and used in the present study. DPI, dry powder inhaler; LCA, life cycle analyses; MCTOC, Montreal protocol Medical and Chemical Options Committee; pMDI, pressurised metered-dose inhaler; SMI, soft mist inhaler.

patients with COPD or asthma can generate sufficient inspiratory flow rate needed for the use of modern DPIs despite the internal resistance of the device.^{3,4} When patients are given a wide range of inhaler options, multi-dose DPIs are the most popular device type.⁵

Currently, pMDIs are the most used inhalers globally, but there are considerable differences between countries and regions. For example, in Sweden DPIs account for 87% of inhalers, while in the UK the majority (70%) of patients use pMDIs.⁶ The UK switched to pMDIs for ICS over the last 10–20 years mainly on cost grounds, even though there was evidence that asthma control deteriorated. Wilkinson *et al* concluded that switching from pMDI to DPI on a national level is not only more environmentally sustainable but could reduce drug costs as well.⁷ High use of DPIs does not seem to hamper overall disease control, indeed asthma control is better than average in some countries with a high proportion of inhaled medication being delivered with DPIs.⁸

As a part of their sustainability programmes, many companies have conducted life cycle analyses (LCA) of their inhaler products including raw material acquisition, processing and manufacturing, distribution and transportation, use, reuse and maintenance and waste management and recycling.⁹ LCA can produce information on many environmental measures such as the carbon footprint, water use, land use, human toxicity, marine toxicity and so on. Carbon footprint is defined as the total global warming potential of greenhouse gases, expressed as carbon dioxide equivalent (CO₂e), emitted into the atmosphere. CO₂e is calculated by multiplying the amount of a greenhouse gas by its global warming potential relative to carbon dioxide. The most commonly used propellants in pMDIs are HFC-134a and HFC-227ea. The sixth IPCC assessment report assigns these gases a 100-year global warming potential (GWP) of 1530 and 3600, respectively.¹⁰ This is a significant increase from the fifth assessment report where they were assigned a GWP of 1300 and 3350 respectively, meaning previous analyses have likely underestimated the true carbon footprint of pMDIs.

Physicians assess benefits and risks for their individual patients, but physicians and patients are increasingly aware of the environmental sustainability of therapeutic choices. This study aims to provide practical information for clinicians prescribing inhalers to treat chronic airway diseases. Hence, we searched all the available LCA data and combined it with inhaler sales data to estimate (1) the overall carbon footprint of inhaler medication use and (2) patient-level carbon footprint of different treatment regimes.

MATERIALS AND METHODS

We conducted a systematic literature search from the databases of medline, biosis, ipa, ddfu, hcaplus, embase and scisearch for inhaler device type or brand associated with terminology used with environmental impact or LCA. Relevant articles were identified also from the reference lists of the articles from the literature search and authors' own files. Some LCA did not include the active pharmaceutical ingredient, and these were excluded from the analysis.

IQVIA data base (IQVIA MIDAS Quarterly, 2020) was searched for sales data for different kinds of inhalers reported as total doses in Europe. Sufficiently accurate data were available from the UK, Germany, France, Spain, Italy, Poland, the Netherlands, Ireland, Belgium, Greece, Czech Republic, Austria, Hungary, Portugal, Norway, Switzerland, Sweden, Finland, Slovakia, Denmark, and Luxemburg.

All calculations on carbon footprint used product-specific information when available and the Montreal Protocol Medical and Chemical Options Committee (MCTOC) assessment report when product-specific LCA was not available. For general calculations of pMDIs, it was assumed that the devices included the more

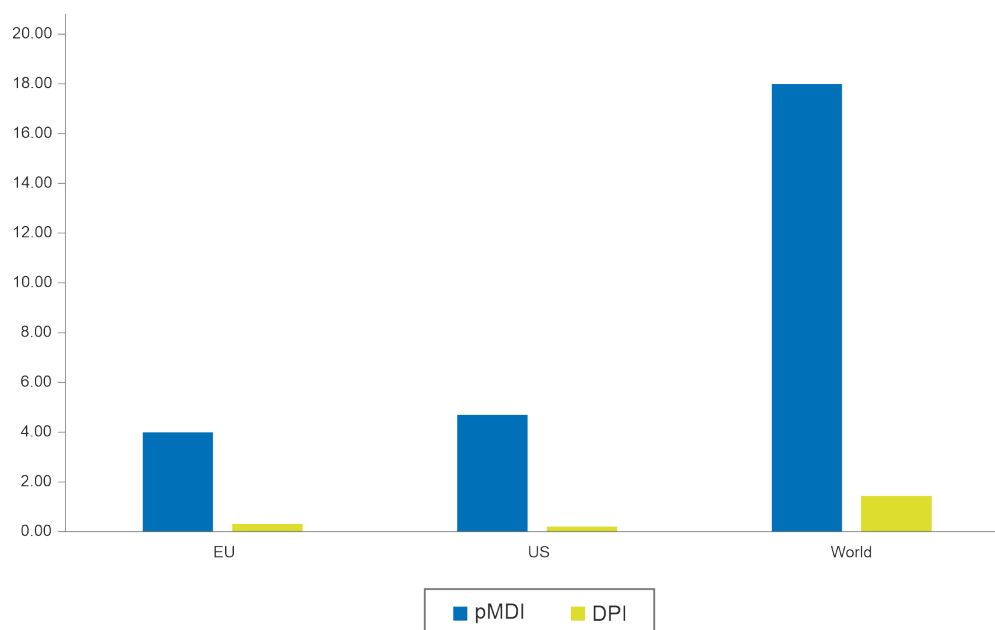


Figure 1 Estimated carbon greenhouse gas emissions from pMDI devices (CO₂e) in EU, EPA estimate for US Emissions and MCTOC estimate for global emissions as well as estimated emissions from corresponding number of DPIs. DPIs, dry powder inhalers; MCTOC, Montreal Protocol Medical and Chemical Options Committee; pMDI, pressurised metered-dose inhalers.

common propellant gas HFA-134a. Treatment regimens used in calculations are those deemed typical by authors according to current summaries of product characteristics and international treatment guidelines.^{11 12}

Patient and public involvement

Patients or public were not involved in the design, conduct or reporting of this work.

RESULTS

Life cycle analyses

The carbon footprint per dose for inhalers with publicly available LCA is presented in [table 1](#).

Inhaler use and corresponding CO₂e emissions

In 2020, the European countries in the IQVIA database used nearly 30 billion doses of pMDI-based medication. Assuming the general estimate of 125 g CO₂e per one dose this amounts to approximately 3.6 million tons (Mt) of CO₂e.² On a national level, the UK was the largest individual source of emissions (44% of total) at approximately 1.3 Mt CO₂e. Assuming emission of 10 g CO₂e per one dose from a DPI (emissions estimated by MCTOC), the equivalent treatment delivered in DPIs would have resulted in net emissions of approximately 0.28 Mt CO₂e for the whole European dataset, and 0.11 Mt CO₂e for the UK, indicating a decrease of 85% compared with pMDI.

In 2020, over 16 000 000 000 doses of salbutamol in pMDI device were sold in the EU, which accounts to more than half of the total pMDI sales. The proportion of salbutamol compared with total pMDI sales ranged from 35% in Sweden up to 67% in the UK. Terbutaline and

fenoterol made negligible contributions compared with salbutamol. The carbon footprint of pMDI salbutamol alone was estimated to be 2.1 Mt CO₂e.

The IQVIA database provided a representative spread of European countries and can be extrapolated to include the whole EU population (UK, Norway and Switzerland are omitted). On 1 January 2020, the population of the EU was estimated to be 447 million and EU countries included in the data accounted for 407 million people.¹³ Scaling by population leads to total pMDI greenhouse gas emissions of 4.0 Mt CO₂e for the EU. Our estimate of EU emissions, United States Environmental Protection Agency (EPA) estimate for US Emissions and MCTOC estimate for global emissions are presented in [figure 1](#).

Patient-level CO₂e emissions of different treatment strategies

The Global Initiative for Asthma (GINA) has recently revised their international recommendations on asthma treatment. Most newly diagnosed patients with asthma start from GINA step 2. The new GINA guidelines include two treatment tracks:

1. In Track 1, for patients at GINA Step 2 it recommends a fixed combination treatment of long-acting β_2 -agonist formoterol with inhaled corticosteroid (LABA/ICS) in a single inhaler taken only as-needed.
2. In the alternative Track 2, for patients at GINA Step 2 the recommendation uses a more traditional strategy of a low-dose maintenance ICS therapy with a separate rescue therapy with short acting β_2 -agonist (SABA).¹¹

To estimate the inhaler use of the patients, we used data from the clinical trial by Bateman *et al* when patients are treated with as-needed budesonide-formoterol (mimicking Track 1 above) compared with

ANNUAL CARBON FOOTPRINT OF TREATMENT AT GINA STEP 2

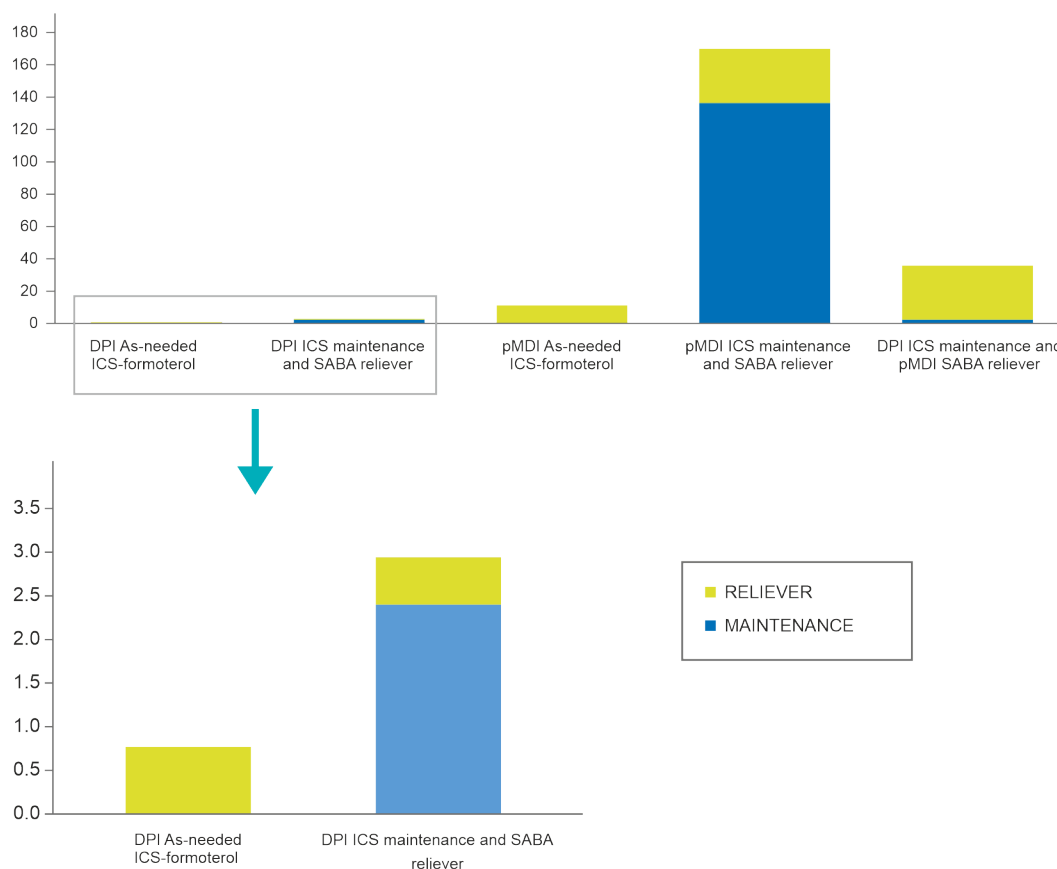


Figure 2 Annual carbon footprint (CO₂e) of different treatment regimens in asthma at GINA step 2. DPI, dry powder inhaler; ICS, inhalable corticosteroid; pMDI, pressurised metered-dose inhaler; SABA, short acting β -2 agonist.

daily maintenance budesonide with as-needed SABA (mimicking Track 2 above). In the study, the patients were using Turbuhaler DPI for all inhaled medications.¹⁴ Since there are thus far no LCA reports available for Turbuhaler, we could not use LCA data specific for Turbuhaler. Instead we used LCA for an Easyhaler DPI since there are published LCA data on Easyhaler for the treatment options in GINA Track 1 and 2 (as described above), and, these LCA are all performed in a single LCA making it internally consistent. In contrast to the study by Bateman *et al*, the SABA used in this analysis was salbutamol instead of terbutaline.

On Track 1, 1 year of treatment with as-needed budesonide-formoterol DPI (0.52 inhalations/day¹⁴) results in greenhouse gas emissions of 0.8 kg CO₂e. On Track 2 above, twice daily maintenance budesonide 200 μ g DPI results in 2.4 kg CO₂e, plus 0.49 doses of as-needed SABA/day¹⁴ results in 0.5 kg CO₂e (a total of 2.9 kg CO₂e per year). The calculation assumes 100% adherence to the maintenance therapy. With the adherence of 1.3 doses per day reported by Bateman *et al*, the carbon footprint would be 1.6 kg CO₂e for the maintenance budesonide and 2.1 kg CO₂e for the maintenance budesonide and SABA together. As the adherence comes from a clinical trial it is likely to overestimate the

adherence in real life. Track 1 had similar exacerbations and lower ICS exposure,¹⁴ but also lower greenhouse gas emissions.

Budesonide with as needed SABA administered from pMDI with similar use as in the study would have resulted in net emissions of 170 kg CO₂e.¹⁴ Figure 2 shows emissions resulting from the two treatment strategies Track 1 and Track 2 of the GINA step 2 with either DPI or pMDI.

Table 2 shows carbon footprint of 1 year of treatment with typical use of inhalers with LCA available. For comparison, estimates of carbon footprint based on MCTOC estimates are presented for some alternative choices. The table can be used to estimate the carbon footprint of inhaler treatment for an individual patient with different combinations of inhalers.

DISCUSSION

In this study, we show that switching from pMDI to DPI substantially reduces the carbon footprint of inhaled treatments. In many countries rescue SABA is almost exclusively delivered by pMDIs, which accounts for over 50% of the carbon footprint of inhaled therapy. Not only does overuse of SABA pose a significant environmental burden,¹⁵ it worsens asthma control, and is associated

Table 2 Carbon footprint of 1 year of treatment with typical use of inhalers with LCA available

One treatment year	DPI or SMI (kg CO ₂ e)	pMDI (kg CO ₂ e)
ICS budesonide 200µg×2	2.4 (Easyhaler)	137 (MCTOC*)
ICS beclomethasone 200µg×2	2.2 (Easyhaler)	60 (Clenil)
LABA/ICS Budesonide/formoterol 320/9×2	2.9 (Easyhaler)	137 (MCTOC*)
LABA/ICS Beclomethasone/formoterol×2	2.8 (NEXThaler)	69 (Foster)
LABA/ICS salmeterol/fluticasone×2	7.0 (Easyhaler)–14.6 (Diskus)	510 (Evohaler)
LAMA 1 canister/month	2.7–9.3 (Respimatt†)	
ICS/LAMA/LABA 1 canister/month		119 (Trimbow)
SABA twice a week‡	0.3 (Easyhaler)	19 (MCTOC*)
SABA 3×200/year‡	1.9 (Easyhaler)	56 (MCTOC*)
SABA 200/month‡	7.4 (Easyhaler)	225 (MCTOC*)
SAMA 1 canister/month		204 (Atrovent)

*Montreal protocol Medical and Chemicals Technical Options Committee.

†SMI instead of DPI.

‡Sufficient disease control, risk of exacerbation and increased mortality according to GINA.¹¹

DPIs, dry powder inhalers; GINA, Global Initiative for Asthma; ICS, inhalable corticosteroid; LABA, long acting β-2 agonist; LAMA, long acting muscarinic agonist; SABA, short acting β-2 agonist; SAMA, short acting muscarinic agonist.SMI, soft mist inhaler;

with asthma deaths. A switch to DPI salbutamol would reduce the carbon footprint for salbutamol by >90% but have no impact on asthma control. However, a switch to DPI combination LABA/ICS for maintenance and rescue would also reduce the overall carbon footprint by 90%, but in addition, substantially improve asthma control. While 100% switch is neither realistic nor desirable, a significant number of patients could use either of the device types. A smaller proportion of subjects switching from pMDI to DPI would create a respective fraction of net saves in green house gas emissions.

It is important that any changes in inhalers and strategy should be done carefully, measured and in partnership with the patient. Non-medical switches (eg, on cost) forced on a population level may lead to deterioration of disease control.¹⁶ Most data on inhaler switching are from open-label marketing-led clinical trials with virtually no real-world data. In a Hungarian study,¹⁷ 143 patients with asthma and 96 with COPD switched their pMDI to a DPI (budesonide–formoterol Easyhaler). After 12 weeks, disease control improved (asthma control test; COPD assessment test), while the annual carbon footprint reduced from 219kg CO₂e to 3kg CO₂e. A UK observational study investigated inhaler switches to save drug costs and found 918 patients who were switched between pMDI and DPI. The authors concluded ‘switching between MDIs and DPIs did not seemingly impact on exacerbations, adverse medication events or respiratory events’. Indeed, the rate of exacerbations was significantly lower in the 3months ‘risk period’ following a switch to DPIs compared with stable periods.¹⁸

The cost of DPIs is often considered to be higher than that of pMDIs, but this largely depends on the specific device being chosen as a replacement. Wilkinson *et al* studied the health economics of inhaler switches based

on NHS prescription data from England in 2017.⁷ Their findings showed that for every 10% of pMDIs that were switched to the cheapest equivalent DPI, the annual drug costs would decrease by 9.4million Euros, whereas retaining the 2017 DPI brand distribution would result in an increase of 14.5million Euros.

LCA are relatively new and still not perfectly validated measures. While there is some standardisation, analyses use a wide variety of assumptions. While analyses are not precisely comparable, they do give an order of magnitude. For example, EU transportation emitted 1100 Mt CO₂e during 2019, around one-third of all emissions. In comparison a typical gasoline-driven car produces annually 4.6 t of CO₂. Nevertheless, in terms of greenhouse gas emissions, switching 90% of the current pMDIs in Europe to DPIs would be equivalent to removing 1.5million cars from the roads.¹⁹ At an individual level, a switch from pMDI to the same medication in a DPI would be similar to changing from a meat to a plant-based diet.²⁰

Due to different methodologies, the EPA estimate for US pMDI emissions and our estimate for EU emissions are not directly comparable, but we can still assess the relative magnitude of the emissions (figure 1). The population of the USA in 2020 was approximately 332million and it would result in the emission of 7.5g CO₂e per capita, while based on our results emissions from EU would be approximately 8.8g CO₂e per capita. While the estimate is not based on full LCA and encompasses only the propellant release in the use phase in the life cycle, in the case of pMDIs this constitutes 94%–98% of the carbon footprint in LCAs.⁶²¹²² As 88% of the inhaler sales in the USA were pMDI devices in 2020 there is a large potential for reduction of emissions.²³ In the UK, Jeswani *et al* estimated emissions from inhalers amount to 1.4 Mt CO₂e which is roughly in line with our results.²² They also

estimate other environmental impacts for pMDIs and one DPI model. The other impacts remain as a largely uninvestigated field as the manufacturers generally have not released third-party certified LCA reports for those. Pernigotti *et al* estimated that if 80% of the pMDI using patients switched to DPIs in UK, Italy, France, Germany and Spain it would lead to 68% decrease inhaler-related carbon footprint.²⁴ If the degree of switch is taken into account, the results are very similar to those of our analysis.

The costs of developing new inhalers (and with established drugs) is enormous. Some companies have moved largely or entirely to soft mist inhaler or DPIs for new inhaled drugs (eg, BI, Novartis). Others (eg, Chiesi, AstraZeneca, GlaxoSmithKline) have announced new low GWP propellant R&D programmes to replace HFC134a in pMDIs. The candidate propellants are HFC-152a²¹ and HFO-1234ze(E). These new inhalers have a carbon footprint almost as low as current DPIs, but will need substantial R&D programmes, the size and length of which depends on the stringency of the safety requirements of the regulatory authorities around the world.²⁵ However, it will likely take a decade or more to roll out any new low GWP propellants to all inhaler brands and drugs.

The Intergovernmental Panel on Climate Change (IPCC) states in its sixth report that without a sharp decline in greenhouse gas emissions by 2030, climate change will lead to irreversible loss of the most fragile ecosystems, and the most vulnerable people and societies will face crisis one after another.²⁶ In healthcare sector, inhaler therapy is a significant source of greenhouse gas emissions globally, which can be easily mitigated through the use of green inhalers at the same time as following guidelines. High standards of care and use of low carbon footprint inhalers are interlinked goals. Low carbon footprint inhalers should be offered to new patients as first choice, unless there is a specific medical reason to choose otherwise.

CONCLUSIONS

Switching from pMDI to DPI substantially reduces the carbon footprint of inhaled treatments. It is now time to act in partnership with patients.²⁷ There is nothing to be gained by waiting.²¹ For those patients who do need an pMDI, low carbon pMDIs will be a very welcome additional transition over the next decade.

Author affiliations

¹Department of Pulmonary Medicine, Helsinki University Hospital Heart and Lung Center, Helsinki, Finland

²University NHS Foundation Trust, UK, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK

³Respiratory Department, East and North Hertfordshire NHS Trust, Stevenage, UK

⁴Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

⁵Department of Allergy and Pulmonary Medicine, University Hospital Iceland, Reykjavik, Iceland

⁶Skin and Allergy Hospital, Helsinki University Hospital, University of Helsinki, Helsinki, Finland

⁷Allergy Centre, Tampere University Hospital, Tampere, Finland

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Contributors VW: conceptualisation, formal analysis, funding acquisition, project administration, visualisation, writing—original draft, and writing—review and editing, acted as the guarantor. AAW: writing—review and editing. AW: writing—review and editing. CJ: writing—review and editing. UB: writing—review and editing. TH: conceptualisation, supervision, writing—review and editing. LL: conceptualisation, supervision, writing—review and editing.

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ORCID iDs

Ville Vartiainen <http://orcid.org/0000-0002-9833-6965>

Alex Wilkinson <http://orcid.org/0000-0002-1808-3663>

Christer Janson <http://orcid.org/0000-0001-5093-6980>

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