The environmental impact of inhaled therapy: making informed treatment choices

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There is increasing interest regarding the carbon footprint of inhaled therapies; while efficacy, safety and patient preference should be prioritised, the increasingly available carbon footprint data may be factored into treatment decision making https://bit.ly/3I6atV2

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Abstract

When selecting the best inhaler and drug combination for a patient with respiratory disease, a number of factors should be considered. While efficacy and safety of medical treatments are always a priority, in recent years the environmental impacts of all aspects of life have become an increasingly necessary consideration and inhaled therapies are no exception. The carbon footprint of an item, individual or organisation is one of the most important and quantifiable environmental impacts, assessed by the amount of greenhouse gases (often expressed in terms of carbon dioxide equivalents) generated throughout the life cycle. The two most commonly prescribed and manufactured inhaler types worldwide are pressurised metered-dose inhalers (pMDIs) containing hydrofluorocarbon (HFC) propellants and dry powder inhalers (DPIs). Most of the carbon footprint of current pMDIs is a result of the propellants that they contain (HFC-134a and HFC-227ea, which are potent greenhouse gases). In comparison, the powder in DPIs is dispersed by the patient's own inhalation, meaning DPIs do not contain a propellant and have a lower carbon footprint than most pMDIs currently available. Soft mist inhalers are another propellant-free option: the device contains a spring, which provides the energy to disperse the aqueous medication. In this review, we examine the published data on carbon footprint data for inhalers, providing an analysis of potential implications for treatment decision making and industry initiatives.

Introduction

When released into the environment, greenhouse gases (GHGs; such as carbon dioxide (CO_2), nitrous oxide (N_2O) and methane (CH_4)) cause global warming by absorbing energy and slowing its release into space [1]. The carbon footprint of an item, individual or organisation typically comprises the life cycle GHG emissions (raw material extraction, production, transportation, utilisation and end-of-life disposal) [2]. This is often stated in "CO_2 equivalents" (CO_2-eq), a unit that expresses the potential global warming effect of all GHG emissions relative to CO_2, allowing comparison [3].

As climate change accelerates, the environmental impact of inhaled therapies is becoming a consideration. A study of inhaler satisfaction and preferences in patients with asthma and chronic obstructive pulmonary disease (COPD) found "environmentally friendly" to be one of the most important characteristics [4]. Patients in a second study, designed to investigate perceived importance of inhaler cost, carbon footprint and ease of use, rated "carbon footprint" as 3.4 out of 5 (where 1="not important" and 5="very

important"); only 14% of patients indicated that carbon footprint was of no importance to them [5]. Despite these findings, little is currently known about how informed patients are on the relative impact of different inhalers. In order to make informed choices that take environmental impact into account, information on the impact of different inhalers needs to be available to patients.

Inhaled therapies are the mainstay of treatments for asthma and COPD [6, 7]. When selecting an inhaled therapy, the efficacy and safety of the inhaler and drug combination is a priority. Discreet choice experiments in patients with asthma or COPD found that the most important factors to the patients were fast onset of relief and a lower rate of exacerbations [8]. The ability of the patient to handle the inhaler and inhale correctly should also be taken into account, to ensure maximum efficacy [9]. When making this decision, it is critical that physicians and patients work together to find the best option.

The two most commonly prescribed and manufactured inhaler types worldwide are dry powder inhalers (DPIs) and pressurised metered-dose inhalers (pMDIs). The majority of the carbon footprint of current pMDIs is a result of the hydrofluorocarbon (HFC) propellants that they contain (HFC-134a and HFC-227ea, which are potent GHGs) [10]. In comparison, DPIs do not require a propellant, as the patient's own inhalation disperses the powder [11]. Soft mist inhalers (SMIs) have emerged as another propellant-free option, as the Respimat device utilises a spring to provide the energy to disperse the aqueous medication. Nebulisers may also be used, although this is typically in an emergency setting or in cases where patients are unable to use pMDIs or DPIs (due to physical or cognitive disabilities) [11], or in patients that healthcare professionals perceive to be at risk of severe symptoms/exacerbations [12]. It is relatively uncommon for nebulisers to be used in an at-home treatment setting and they only account for around ⩽10% of the market (on a dose basis) [13]; a comparative study of a nebuliser *versus* an HFC-134a pMDI found the carbon footprint of the nebuliser to be significantly lower [14].

There are an increasing number of global and national initiatives addressing the environmental impact of inhaled therapies. In 1987, the Montreal Protocol decreed that production and consumption of ozone-depleting substances should be phased out [15]. This included chlorofluorocarbons (CFCs), which are not only ozone depleting but also have an extremely high global warming potential (GWP) [16]. The phase-out of CFCs for ozone layer protection has also had a much greater incidental benefit on climate than was previously realised: avoided damage to the ozone layer has reduced ultraviolet damage to vegetation, in turn increasing the Earth's terrestrial carbon stores [16].

The GWP of a gas is an indication of the amount of warming it causes over a specified period of time (typically 100 years) relative to CO_2; CO_2 has an index GWP value of 1 and all other GWPs are a multiplication of this [3]. For example, CFC-12 (previously used as a propellant in pMDIs) has a GWP of 10 200 [17]. To replace CFCs as propellants in inhalers, ozone-safe HFCs, such as HFC-134a and HFC-227ea, were introduced, but these are GHGs with GWPs of 1300 and 3350, respectively [17]. HFC-152a is a new propellant under early development with a lower GWP (138) compared with existing propellants [10, 17]. These HFCs (HFC-134a, HFC-227ea and HFC-152a) will be progressively phased down under the Kigali Amendment to the Montreal Protocol [13]. The initial launch of the first HFC-152a pMDI is projected for around 2025 [18, 19]. A hydrofluoroolefin (HFO) with a low GWP (<1), HFO-1234ze(E), is also currently under early development as an alternative propellant in pMDIs [13] and is not subject to phase-down under the Kigali Amendment to the Montreal Protocol.

As a result of the high GWPs of HFC-134a and HFC-227ea, their use in pMDIs was responsible for direct emissions of ~18 000 000 tonnes CO_2-eq in 2018, which was ~0.03% of the total global GHG emissions for that year [13, 20]. In terms of CO_2-eq emissions, a single two-puff dose of an HFC-134a pMDI is comparable to everyday items such as a 330 mL can of cola or 2 km driven in a Seat Ibiza Ecomotive [13]. Therefore, in addition to international policies such as the Montreal Protocol, some national organisations have now made commitments to reduce carbon emissions resulting from inhaler use. For example, the National Health Service (NHS) in the UK aims to be entirely carbon neutral by 2045 [21]. In England, pMDI use accounts for 13% of NHS carbon emissions related to delivery of care and 3% of total NHS carbon emissions (the majority of which is a result of pMDI propellants) [21, 22]. To put this into context, this is equivalent to the carbon emissions resulting from all the electricity used by the NHS (3%) [21, 22]. As one of the measures to help achieve this target, the Sustainable Development Unit of the NHS aims to reduce carbon emissions resulting from pMDIs by encouraging the use of "lower carbon inhalers, such as DPIs" [21]. Additionally, the British Thoracic Society has committed to reduce the carbon footprint of inhaled therapies, also recommending the prescription of "low carbon alternatives" to pMDIs, such as DPIs and reusable SMIs [23].

In this review, we examine the currently available carbon footprint data for inhaled therapies and assess potential implications for treatment decision making and industry initiatives. The aim of the review is to assemble findings that provide valuable insight for a number of audiences, including patients who wish to factor in the environmental impact of their inhalers when making treatment decisions, healthcare professionals who want to help patients make informed decisions, companies aiming to reduce the impact of their supply chain and policy makers who wish to reduce the impact of healthcare systems.

How can the environmental impact of inhalers be assessed?

A life cycle assessment (LCA) is a systematic evaluation of the environmental impact of any item or product, across its entire life cycle (figure 1) [2]. LCAs are typically carried out with a specific goal or strategy in mind, *e.g.* a pharmaceutical company may be seeking to identify opportunities within their value chain to reduce their environmental impact [24]. As part of an LCA, a number of environmental impacts must be assessed. Examples include climate change impact, human toxicity, fossil depletion, marine eutrophication and ozone depletion, as well as the relative contribution of various device elements (such as plastics or aluminium) to these impacts [10].

There are a number of methods that may be used to carry out carbon footprint assessments, including the GHG Protocol Product Life Cycle Accounting and Reporting Standard or International Organization for Standardization (ISO) 14067 [2, 25]. These international standards provide the benchmark for organisations to quantify the environmental impact of products and prepare GHG emissions inventories.

Carbon footprint data for inhaler devices

The carbon footprints of a number of inhalers, including both pMDIs and DPIs, have been assessed and published. The methodology and guidelines adopted in these various studies were not consistent. For this review, we present the methodology (table 1) and results (table 2) of these studies, based on published available information [10, 25–35].

Studies comparing pMDIs with DPIs

The Carbon Trust conducted an independent carbon footprint assessment on behalf of GlaxoSmithKline (GSK) and evaluated three combination therapies: fluticasone furoate/vilanterol (FF/VI) 92/22 µg DPI (Relvar Ellipta), salmeterol xinafoate/fluticasone propionate (SAL/FP) 50/500 µg Accuhaler DPI (Diskus) and SAL/FP 25/250 µg HFC-134a pMDI (figure 2a) [26]. Per month of treatment, the carbon footprints of each inhaler are shown in table 2: a large proportion of the carbon footprints for SAL/FP 50/500 µg and FF/VI 92/22 µg DPIs resulted from the manufacture of the devices and the active pharmaceutical ingredients (APIs). In contrast, for SAL/FP 25/250 µg HFC-134a pMDI, 74% of the much larger carbon footprint resulted from the propellant alone.

Jeswani and Azapagic [10] compared a DPI (Diskus) *versus* HFC pMDIs containing three different propellants (HFC-134a, HFC-227ea and HFC-152a). The assessment included the production of the device and propellants (for pMDIs), inhaler use, and end-of-life disposal; APIs were not considered. Jeswani and Azapagic [10] estimated that if all prescribed pMDIs in the UK were replaced by currently available DPIs

FIGURE 1 The stages involved in a cradle-to-grave life cycle assessment [2].

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TABLE 1 Summary of methodology used in studies on the carbon footprint of inhalers

	Carbon Trust [26]	Jeswani and Azapagic [10]	Panigone *et al.* [27]	Hänsel *et al.* [28]	Orion Pharma [29, 30]	Aumônier *et al.* [31]
Inhaler and drug combination(s) studied (pack size)	• FF/VI 92/22 µg DPI (Relvar Ellipta; 30-day) • SAL/FP 50/500 µg Accuhaler DPI (Diskus; 30-day) • SAL/FP 25/250 µg pMDI (30-day)	Inhaler devices only, API not considered: • DPI (Diskus) (60-dose) • HFC-134a pMDI (100-dose/200 act) • HFC-227ea pMDI (60-dose/120 act) • HFC-152a pMDI (100-dose/200 act)	• FORM/BDP NEXThaler 6/100 µg DPI (120-dose)[#] • FORM/BDP 6/100 µg pMDI (120-dose)[#]	• TIO Respimat SMI (both disposable and reusable; 60 act per month) • IB/FEN Respimat SMI (120 act per month) • IB/FEN HFC pMDI (200 act per month) • IB HFC pMDI (200 act per month)	Easyhaler DPI: • BUD/FORM 160/4.5 µg (120-dose) • SAL/FP 50/250 µg (60-dose) • SALB 100 µg (200-dose) • FORM 12 µg (120-dose)	Breezhaler DPI: • IND/GLY/MF (30-day) +sensor • IND/GLY/MF (30-day) • IND/GLY/MF (90-day) • IND/MF (30-day)
Method and standard(s) applied	PAS 2050, GHG Protocol Product Standard Sector Guidance [25], Carbon Trust Footprint Expert tool	ISO 14040 and ISO 14044 (multiple environmental impacts appraised) [32, 33]	ISO 14067 and GHG Protocol Product Standard Sector Guidance [2, 34]	IPCC Fifth Assessment Report on Climate Change, GHG Protocol Product Life Cycle Accounting and Reporting Standard and Standard Sector Guidance [25, 34, 35]	Analysis conducted by Carbon Footprint Ltd in accordance with ISO 14067 (multiple environmental impacts appraised) [2]	Streamlined LCA completed in accordance with the GHG Protocol Product Accounting and Reporting Standard using Sector Guidance for Pharmaceuticals and Medical Devices [25, 34]
Assurance/ certification	Individual product carbon footprints certified by Carbon Trust as compliant with the above standards; certification report published	None	Third party (not named); the calculation tool/procedure (CF-S) is stated as certified; product footprints reported as being certified to the above standards	Not disclosed	Analysis conducted by Carbon Footprint Ltd (ISO 14001:2015 and 9001:2015 certified)	Critically reviewed/verified by third party (representative from Resource and Waste Solutions); certification report available
Life cycle stages included						
Raw material extraction	✓	✓	✓	✓	✓	✓
Production of device	✓	✓	✓	✓	✓	✓
Production of API	✓	X	✓	✓	✓	✓
Production of final product	✓	✓	✓	✓	✓	✓
Packaging	✓	X	✓	✓	✓	✓
Distribution and storage	✓	✓	✓	✓	✓	✓
Pharmacy/retail	X	X	X	Not stated	Not stated	X
Patient travel	Not stated	X	Not stated	Not stated	Not stated	X
Patient use	✓	✓	✓	✓	Not stated	X
End-of-life disposal	✓	✓	✓	✓	✓	✓

SAL: salmeterol; FP: fluticasone propionate; pMDI: pressurised metered-dose inhaler; FF: fluticasone furoate; VI: vilanterol; DPI: dry powder inhaler; API: active pharmaceutical ingredient; HFC: hydrofluorocarbon; act: actuations; FORM: formoterol; BDP: beclometasone dipropionate; TIO: tiotropium bromide; SMI: soft mist inhaler; IB: ipratropium bromide; FEN: fenoterol hydrobromide; BUD: budesonide; SALB: salbutamol; IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate; PAS: Publicly Available Specification; GHG: Greenhouse Gas; ISO: International Organization for Standardization; IPCC: Intergovernmental Panel on Climate Change; LCA: life cycle assessment. [#]: other drug/device combinations investigated in this study have not been discussed here.

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TABLE 2 Summary of results of studies investigating the carbon footprint of inhalers

	Carbon Trust [26]	Jeswani and Azapagic [10]	Panigone *et al.* [27]	Hänsel *et al.* [28]	Orion Pharma [29, 30]	Aumônier *et al.* [31]
Inhaler and drug combination(s) studied (pack size)	Full life cycle appraised: • FF/VI 92/22 µg DPI (Relvar Ellipta; 30-day) • SAL/FP 50/500 µg Accuhaler DPI (Diskus; 30-day) • SAL/FP 25/250 µg pMDI (30-day)	Inhaler devices only, API not considered: • DPI (Diskus) (60-dose) • HFC-134a pMDI (100-dose/200 act) • HFC-227ea pMDI (60-dose/120 act) • HFC-152a pMDI (100-dose/200 act)	Full life cycle appraised • FORM/BDP NEXThaler 6/100 µg DPI (120-dose)[#] • FORM/BDP 6/100 µg pMDI (120-dose)[#]	Full life cycle appraised: • TIO Respimat SMI (disposable; 60 act per month) • IB/FEN Respimat SMI (120 act per month) • IB/FEN HFC pMDI (200 act per month) • IB HFC pMDI (200 act per month)	Full life cycle appraised: Easyhaler DPI: • BUD/FORM 160/4.5 µg (120-dose) • SAL/FP 50/250 µg (60-dose) • SALB 100 µg (200-dose) • FORM 12 µg (120-dose)	Full life cycle appraised: Breezhaler DPI: • IND/GLY/MF (30-day) +sensor • IND/GLY/MF (30-day) • IND/GLY/MF (90-day) • IND/MF (30-day)[¶]
Carbon footprint, kg CO_2-eq per month	• FF/VI 92/22 µg DPI: 0.765 • SAL/FP 50/500 µg Accuhaler DPI (Diskus): 1.250 • SAL/FP 25/250 µg pMDI: 20.370	• DPI (Diskus): 1.08[+] • HFC-134a pMDI: 31.56[+] • HFC-227ea pMDI: 83.64[+] • HFC-152a pMDI: 2.4[+]	• FORM/BDP NEXThaler 6/100 µg DPI: 0.916[+] • FORM/BDP 6/100 µg pMDI: 11.33[+]	• TIO Respimat SMI (disposable): 0.775 • IB/FEN Respimat SMI: 0.784 • IB/FEN HFC pMDI: 16.484 • IB HFC pMDI: 14.585	Easyhaler DPI: • BUD/FORM 160/4.5 µg: 0.514 • SAL/FP 50/250 µg: 0.602 • SALB 100 µg: 0.664 for total life cycle[§] • FORM 12 µg: 0.287[f]	Breezhaler DPI: • IND/GLY/MF (30-day) +sensor: 0.481 • IND/GLY/MF (30-day): 0.359 • IND/GLY/MF (90-day): 0.184
Main contributor(s) to total carbon footprint	• FF/VI 92/22 µg DPI: manufacture of device and final product (90% of total carbon footprint (47% device manufacture, 43% manufacture of final product)) • SAL/FP 50/500 µg Accuhaler DPI (Diskus): API and device production (77% of total carbon footprint (48% API production, 29% device production)) • SAL/FP 25/250 µg pMDI: propellant (74% of total carbon footprint (56% during use, 18% at end-of-life disposal))	• HFC-134a pMDI: propellant emissions during use (~99% of total carbon footprint) • HFC-227ea pMDI: propellant emissions during use (~80% of total carbon footprint) • HFC-152a pMDI: propellant emissions during use (~80% of total carbon footprint) • DPI (Diskus): raw materials and device manufacture (~90% of total carbon footprint)	• FORM/BDP NEXThaler 6/100 µg DPI: manufacture of device and packaging (57.9% of total carbon footprint (32.2% device packaging, 25.7% energy and water consumption during manufacture)) • FORM/BDP 6/100 µg pMDI: propellant (92.5% of total carbon footprint (70.2% during use, 22.3% at end-of-life disposal))	• TIO Respimat SMI (disposable) and IB/FEN Respimat SMI: manufacture of device and cartridge (~90% of total carbon footprint (~60% device materials and production energy, ~30% cartridge materials and production energy)) • IB/FEN HFC pMDI and IB HFC pMDI: propellant (~98% of total carbon footprint)	• Easyhaler DPI[##]: device manufacture (54–65% of total carbon footprint)	• Breezhaler DPI[##]: manufacture of API, device and packaging; where sensor was included, the sensor raw materials were the main contributor

SAL: salmeterol; FP: fluticasone propionate; pMDI: pressurised metered-dose inhaler; FF: fluticasone furoate; VI: vilanterol; DPI: dry powder inhaler; API: active pharmaceutical ingredient; HFC: hydrofluorocarbon; act: actuations; FORM: formoterol; BDP: beclometasone dipropionate; TIO: tiotropium bromide; SMI: soft mist inhaler; IB: ipratropium bromide; FEN: fenoterol hydrobromide; BUD: budesonide; SALB: salbutamol; IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate; CO_2-eq: carbon dioxide equivalents. [#]: other drug/device combinations investigated in this study have not been discussed here; [¶]: carbon footprint of these devices not included in the respective reference; [+]: calculated based on a dosage of 120 actuations per month (two actuations twice daily for 30 days); [§]: monthly carbon footprint data not provided by reference and not calculated by the authors of this paper due to expected variation resulting from as-needed use by patient; [f]: value assumes maintenance use (for more severe disease, dose and emissions are doubled); [##]: the main contributor(s) to the carbon footprint were not specified per product in this reference.

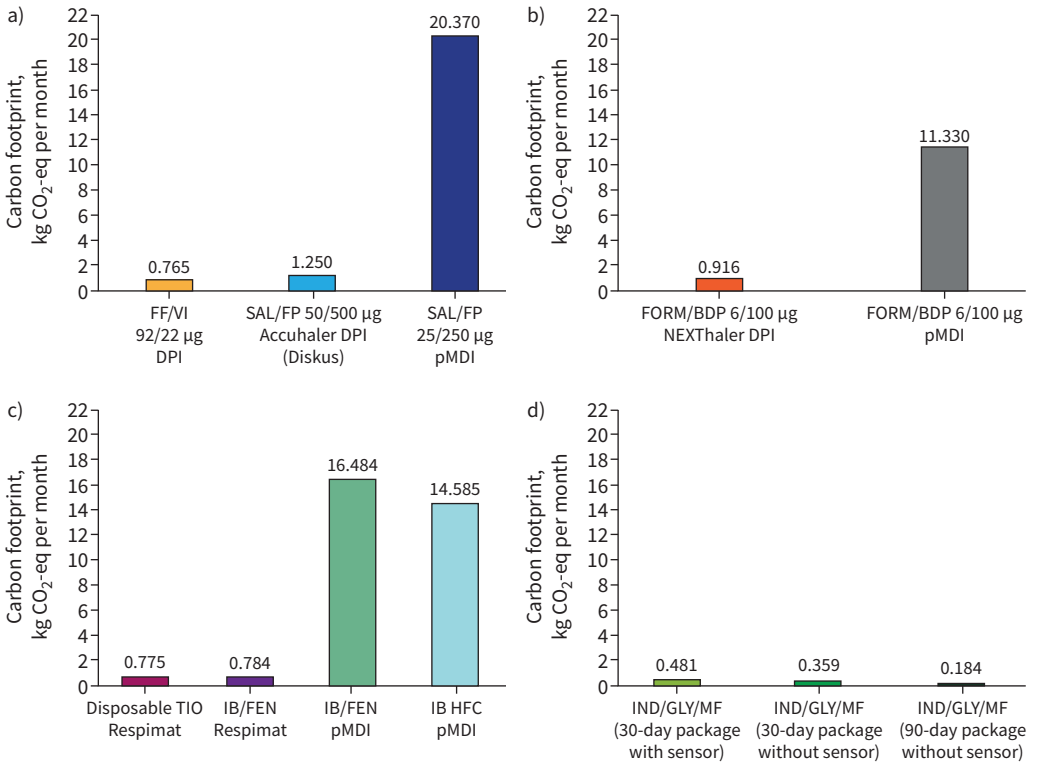

FIGURE 2 Carbon footprint (carbon dioxide equivalents (CO_2-eq)) per month for a) FF/VI 92/22 µg DPI, SAL/FP 50/500 µg Accuhaler DPI (Diskus) and SAL/FP 25/250 µg pMDI (API included) [26], b) FORM/BDP 6/100 µg as NEXThaler DPI *versus* pMDI (API included) [27], c) disposable TIO Respimat SMI, IB/FEN Respimat SMI, IB/FEN HFC pMDI and IB HFC pMDI (API included) [28], and d) Breezhaler IND/GLY/MF devices (API included) [31]. SAL: salmeterol xinafoate; FP: fluticasone propionate; FF: fluticasone furoate; VI: vilanterol; DPI: dry powder inhaler; pMDI: pressurised metered-dose inhaler; API: active pharmaceutical ingredient; FORM: formoterol; BDP: beclometasone dipropionate; TIO: tiotropium; SMI: soft mist inhaler; IB: ipratropium bromide; FEN: fenoterol hydrobromide; HFC: hydrofluorocarbon; IND: indacaterol acetate; GLY: glycopyrronium bromide; MF: mometasone furoate.

(assuming 9 g CO_2-eq per dose), the estimated reduction in carbon footprint would be 96%. The theoretical future replacement of all HFC-227ea (697 g CO_2-eq per dose) and HFC-134a (263 g CO_2-eq per dose) pMDIs by those containing HFC-152a (assuming 20 g CO_2-eq per dose; first product projected for release in 2025 [18, 19]) could result in a 92% reduction in carbon footprint [10]. However, they suggested that the substitution of current pMDIs with some disposable DPIs (Diskus) could result in the worsening of some other environmental impacts, which is likely due to their large plastic and aluminium content.

Panigone *et al.* [27] assessed the carbon footprint of combination formoterol/beclometasone dipropionate (FORM/BDP) 6/100 µg in the NEXThaler DPI *versus* an HFC-134a pMDI formulation. Based on 1 month's treatment, the DPI had a carbon footprint of 0.916 *versus* 11.330 kg CO_2-eq for the pMDI, meaning 1 month's pMDI use was approximately equivalent to a year of DPI use (table 2 and figure 2b) [27]. For the DPI, energy and water consumption during manufacture and the device packaging had the biggest impacts on the carbon footprint. The majority of the considerably larger carbon footprint of the pMDI was due to the HFC-134a propellant, with 92.5% of total emissions arising from the use phase and end-of-life disposal (table 2).

Study comparing SMIs versus *pMDIs*

Unlike pMDIs, Respimat (which is an SMI) does not require a propellant: a spring provides the energy to dispense an aqueous solution as a mist of particles that can be inhaled slowly [36].

Hänsel *et al.* [28] carried out a study comparing the carbon footprint of Respimat SMI *versus* pMDIs for several drug combinations: reusable tiotropium (TIO) Respimat, disposable TIO Respimat, combination

ipratropium bromide/fenoterol hydrobromide (IB/FEN) Respimat, combination IB/FEN pMDI (HFC-134 propellant) and monotherapy IB HFC pMDI (also HFC-134 propellant) (figure 2c and table 2). This study did not include a comparison with the TIO Handihaler DPI (also produced by Boehringer Ingelheim), which would have been useful for a full evaluation of the relative environmental impact. Table 2 and figure 2c show the carbon footprints, per month, of each of the devices included in the study [28]. Switching from an HFC pMDI to a disposable SMI would result in ∼95% reduction in life cycle carbon footprint, a similar reduction to a switch to a DPI [10, 28]. Compared with the disposable device over 1 month, use of the reusable TIO Respimat over 3 months would further reduce the monthly carbon footprint to 0.34 kg CO_2-eq (corresponding to a 57% reduction) or 0.23 kg CO_2-eq if used over 6 months (a 71% reduction).

Studies including DPI comparisons

Easyhaler (DPI) products were assessed in a cradle-to-grave study by Carbon Footprint Ltd on behalf of Orion Pharma [29, 30]. Table 2 shows the carbon emissions, per month, for the maintenance products included in the study [30]. The total life cycle emissions for a 200-dose salbutamol (SALB) 100 µg DPI equated to 0.664 kg CO_2-eq [30].

An LCA, including a carbon footprint evaluation, has been conducted to assess the environmental impact of two Breezhaler (DPI) products: one containing indacaterol acetate (IND) and mometasone furoate (MF) and the other IND, glycopyrronium bromide (GLY) and MF as fixed-dose combinations. Comprehensive data were produced for 30-day (both products) and 90-day (IND/GLY/MF) packages, with and without an inspiratory sensor (IND/GLY/MF) [31, 37]. Table 2 and figure 2d show carbon footprint values, per month, for the devices included in the study [31].

pMDIs using HFC-227ea

There are no published life cycle analyses of HFC-227ea-containing pMDIs that we are aware of; however, multiple lines of evidence help to indicate the approximate carbon footprint of these inhalers. A FP/FORM pMDI is known to use 11 g of HFC-227ea [38], which is equivalent to a carbon footprint of 36.85 kg CO_2-eq for the propellant alone (based on the GWP of HFC-227ea) [17]. Jeswani and Azapagic [10] estimated the carbon footprint of an HFC-227ea pMDI to be 0.70 kg CO_2-eq per dose compared with 0.26 kg CO_2-eq with an HFC-134a pMDI. These values are in line with estimates in the Montreal Protocol 2018 report, which quoted a range of 0.6–0.8 kg CO_2-eq per dose for HFC-227ea pMDIs and 0.2–0.3 kg CO_2-eq for HFC-134a pMDIs [13].

Of the products shown in figure 2, the inhaler with the greatest carbon footprint (SAL/FP 25/250 µg pMDI) has monthly emissions in the region of a 100 times greater than the inhaler with the lowest carbon footprint (IND/GLY/MF DPI 90-day pack without sensor) [26, 31]. Values presented by Jeswani and Azapagic [10] have not been included in this calculation, as the values were not presented for specific drug/device combinations; however, if the HFC-227ea device were included, even without API inclusion, carbon footprint values would be far greater than even the SAL/FP 25/250 µg pMDI. Of the DPIs studied, there was a seven-fold increase in monthly emissions between the inhaler with the highest carbon footprint (SAL/FP 50/500 µg DPI) *versus* the DPI with the lowest footprint [26, 31]. Although direct head-to-head studies have not been conducted, similar methodologies were used. Nevertheless, direct comparisons should be interpreted with caution until head-to-head studies have been completed.

Discussion

GHGs cause global warming by absorbing energy and slowing its release into space [1]. The resulting climate change is associated with increased exposure to pollution and aero-allergens (such as pollen), among other impacts [39, 40]. This is likely to exacerbate respiratory diseases such as asthma, with an associated increase in rescue medication use [39–42]. As climate change accelerates, the global community is increasingly seeking to minimise avoidable production and use of GHGs, such as HFCs.

There are clear differences in the carbon footprints of various inhalers [10, 26–29, 31]. We have reviewed the published literature on the carbon footprint of inhalers and have identified a difference of up to 100-fold between lower carbon DPIs/SMIs and HFC-134a pMDIs. This difference can be as much as 200-fold when comparing lower carbon DPIs/SMIs with HFC-227ea pMDIs (based on the GWP of HFC-227ea propellant) [10, 31]. In pMDIs, the current HFC propellants (HFC-134a and HFC-227ea; GWPs of 1300 and 3350, respectively) account for >90% of the overall product carbon footprint [10]. Furthermore, the carbon footprint of different HFC-134a salbutamol pMDI brands can vary substantially: Ventolin pMDIs contain an estimated 17.32–19.8 g of HFC-134a *versus* 6.68–8.5 g of HFC-134a in a

Salamol pMDI, which suggests that switching to Salamol would correspond to an estimated saving of 18 kg CO_2-eq per inhaler [43].

To the best of our knowledge, pMDIs containing HFC-227ea propellants have not yet been subjected to a formal LCA of their carbon footprint, although this is almost three-fold worse than HFC-134a pMDIs according to relative propellant GWPs [10]. The carbon footprint of prescribed inhalers could be reduced by switching from current pMDIs to current DPIs or SMIs. DPIs have a carbon footprint per month of only 3.4% of an HFC-134a pMDI and just 1.3% of an HFC-227ea pMDI (without consideration of the API) [10]. When the API is included, one study found that per actuation, a DPI had a carbon footprint of 8.1% of an HFC-134a pMDI delivering the same medication [27]. Furthermore, JANSON *et al*. [44] calculated that if UK prescribing patterns were matched to those of Sweden, where 90% of prescribed inhaled corticosteroid devices are DPIs, this would result in an annual reduction of 550 000 tonnes CO_2-eq.

If successful research and development leads to the introduction of lower GWP propellants such as HFC-152a or HFO-1234ze(E) (GWPs of 138 and <1, respectively [17]), this could reduce the carbon footprint of pMDIs substantially. For example, replacing HFC-227ea and HFC-134a with HFC-152a (scheduled to be introduced in the first pMDIs in 2025 [18, 19]) could reduce the carbon footprint of pMDIs in the UK by 92% [10], mainly in inhalers containing short-acting β_2-agonists (SABAs). Further research is needed on the life cycle carbon footprint of HFC-152a pMDIs. However, on the basis of the GWP alone, the utilisation of HFC-152a could result in ∼10–20-fold improvement *versus* current pMDIs [17], although they are still likely to have a higher carbon footprint than DPIs [10, 45].

It is difficult to make precise comparisons between studies on the relative carbon footprints of inhalers, due the different methodologies employed [2, 24]. However, in general, all DPIs and SMIs have a substantially lower carbon footprint than pMDIs. Further environmental benefits may come from reusable inhalers [28] and through longer treatment packs (*e.g.* 90-day instead of 30-day options) [31].

Poor treatment adherence to controller therapy can lead to an increase in the overall carbon footprint, as inhaled rescue medication is typically delivered *via* high-GWP salbutamol pMDIs. The use of rescue salbutamol pMDIs in Italy, Spain, France, Germany and the UK is estimated to produce 1 791 312 tonnes CO_2-eq per year, of which 250 000 tonnes is a result of SABA overuse (prescription of ⩾3 canisters per year *versus* 0–2) in the UK alone [46]. A new trend for the addition of inspiratory sensors will result in a small increase in carbon footprint [31, 37], but this could be offset by improved patient adherence in the real world [47] and resulting reductions in rescue medication use.

In children with poorly controlled asthma, improved adherence from using a Smartinhaler device with budesonide (BUD)/FORM 200/6 µg DPI led to a reduction in overall GHG emissions of ∼50% (due to reduced reliever use, as well as fewer hospital admissions and associated travel) [48]. In addition, waste production and water consumption were reduced by ∼60% and ∼32%, respectively (also largely due to reductions in hospital admissions and associated travel). In the real-world Salford Lung Study in Asthma (SLS Asthma), randomisation to a once-daily combination FF/VI in a DPI improved asthma control and led to a 10% reduction in rescue salbutamol pMDI use (over the course of 1 year) compared with usual care [49]. Using sustainable quality improvement methodology and NHS Sustainable Development data, it was calculated that patients randomised to FF/VI in SLS Asthma had a significant saving in their carbon footprint compared with standard care (141 kg CO_2-eq per patient per year in the FF/VI arm), alongside improvements in clinical outcomes [50].

The carbon footprint of an inhaler is one variable to consider when patients make informed treatment decisions. However, in practice, most patients have little knowledge of the carbon footprint of their inhaler. Other factors include cost, patient preference, physician "custom and practice" and most importantly, the ability of the patient to use their inhaler correctly.

With variability in oropharyngeal deposition due to particle size, resistance, speed of aerosol, as well as inhalation technique, it is difficult to compare therapeutic efficacy between pMDIs and DPIs. Poor inhaler technique may be a key contributor to the economic burden of managing asthma and COPD [23, 51]. Many patients have difficulty with the coordination required for correct pMDI use and find DPIs easier to use correctly [52]. Patients with very limited lung function (very young, very old or with an exacerbation) may not achieve the theoretical inspiratory flow needed to get the full dose from high-resistance DPIs [53–55]. However, the majority of patients are able to generate a sufficient inspiratory flow to use low-resistance DPIs [53, 54]. In addition, for SABAs, the change in forced expiratory volume in 1 s following a 50 or 400 µg dose of salbutamol is similar [56], suggesting that a suboptimal inhalation may

still provide adequate bronchodilation. Further study is needed to determine whether there are patients with lower therapeutic responses at equivalent doses from DPIs *versus* MDIs. Recently, the importance of the context of testing novel drugs and inhalers and the characteristics of the patient groups studied has emerged as important; studies on ideal patients in clinical trials for regulatory purposes or for marketing may have little relevance to patients in usual clinical practice [57].

Availability and affordability are major considerations in inhaler choice and adherence. The majority of HFC use in inhalers comes from salbutamol pMDIs, which are significantly cheaper than multidose DPIs (per dose) [13]. In low-income or developing countries, treatment decisions are likely to be largely driven by cost, making carbon footprint a low priority for the patient. In such countries, pMDIs are often relatively inexpensive and therefore more widely used. For example, in Uganda, only salbutamol pMDIs meet the specified criteria for affordability: an analysis demonstrated that salbutamol 100 µg pMDIs cost 2 days' wages (of the least paid government employee) while the two DPIs containing inhaled steroids for which data were available (BUD 200 µg and FP 125 µg) cost 8 and 10 days' wages, respectively [58]. However, in some developing countries, single-dose DPIs are most commonly used, as they only require simple manufacturing technology and can be purchased for a relatively low cost [13].

In high-income countries, the relative cost to the patient of pMDIs and DPIs varies greatly and is related to market factors. Based on global prescribing data, one study found that combination long-acting β-agonist/inhaled corticosteroid therapy is significantly more expensive as a DPI *versus* pMDI in the USA and Puerto Rico, but is >10% cheaper in the UK, Canada and Australia [53]. The country of production also has a large impact on the cost of devices: imported devices manufactured by multinational companies situated in developed countries are typically more expensive than devices produced locally or imported devices manufactured by multinational companies situated in developing countries. In the future, the cost of HFC propellants is expected to increase as HFC use decreases in other nonmedical settings, potentially increasing the relative cost of pMDIs *versus* DPIs [53]. The cost per kilogram of HFC-152a is currently comparable to that of HFC-134a [53], although it is not yet commercialised in inhalers, and the potential future market and cost implications for HFC-152a in nonmedical applications (*e.g.* industrial settings) are unknown.

The environmental impact of inhalers should be factored into treatment decision making by patients and healthcare professionals, along with other aspects such as ease of use and the ability of patients to inhale correctly. To help inform patients and facilitate these discussions, patient decision aids could be used. However, at present, there are very few options available and they do not sufficiently cover the environmental impact of inhalers, if at all [59, 60]. For example, the National Institute for Health and Care Excellence (NICE) in the UK has developed a patient decision aid which includes questions and information around the carbon footprint of various inhalers (figure 3) [60]. This discussion comes after the decision has been made to use a specific inhaler and the inhalation technique optimised. The decision aid gives no sense of the magnitude of the difference in carbon footprint and so does not assist decision making on environmental grounds. This highlights the need for decision aids that allow patients and clinicians to assess environmental impact and enable them to make an informed treatment choice. It is important that when such discussions take place, patients should not be made to feel guilt or pressure for the environmental impact of their inhaler choice, if this leads to detrimental effects on adherence and therefore disease control and quality of life [61].

From industry and government perspectives, a number of pharmaceutical companies and national healthcare organisations have now developed "Net Zero" commitments with the aim of reaching zero carbon emissions across their operations [21, 62–64]. For those companies manufacturing current HFC MDIs, these can account for a substantial proportion of the entire company's carbon footprint. For example, the most recently published values indicate that pMDI use accounts for 13% of total carbon emissions for AstraZeneca and 36% for GSK [65, 66]. By reducing or eliminating HFC pMDIs within their inventory and replacing with inhalers with lower carbon footprints, such as DPIs or pMDIs containing new lower GWP propellants, companies would be able to achieve a lower carbon footprint. Pharmaceutical companies can use the outputs of carbon footprint studies to inform investments that address the overall environmental impact of inhaler production, such as the adoption of DPIs, development of lower carbon propellants for pMDI devices, development of technologies such as SMIs, longer lasting or recyclable devices, manufacturing processes that minimise fossil fuel consumption and impact on ecotoxicity.

In order to select the most appropriate inhaled therapy for the patient, efficacy and safety should always be prioritised. A number of additional factors must be considered, including patient history and preference,

Summary 2	BAI	DPI	pMDI	pMDI with spacer
Do I need to clean it? Pg. 10	Yes, the plastic casing needs cleaning	Yes, the mouthpiece needs cleaning	Yes, the mouthpiece and plastic casing needs cleaning	Yes, the mouthpiece, plastic casing and the spacer all need cleaning
How big is it? Pg. 11	It is larger than a pMDI but may fit into your pocket	It is larger than a pMDI but may fit into your pocket	It is small and usually fits into your pocket	The pMDI is small and usually fits into your pocket. The spacer is bigger and cannot fit into your pocket
What is the carbon footprint of the inhaler? Pg. 12	It contains propellant, so it has a higher carbon footprint than a DPI	It does not contain propellant, so it has a lower carbon footprint than the other inhalers	It contains propellant, so it has a higher carbon footprint than a DPI	It contains propellant, so it has a higher carbon footprint than a DPI
Can it be recycled? Pg. 13	Yes, at some local pharmacies	Yes, at some local pharmacies	Yes, at some local pharmacies	**pMDI:** Yes, at some local pharmacies **Spacer:** This cannot currently be recycled

FIGURE 3 The carbon footprint of inhalers referenced in a summary of different factors related to using inhalers and how they compare with each other in the National Institute for Health and Care Excellence (NICE) patient decision aid for inhalers for asthma ([60], p. 8). BAI: breath-actuated metered-dose inhaler; DPI: dry powder inhaler; pMDI: pressurised metered-dose inhaler.

patient ability and dexterity, and costs to the patient [13]. There is a growing interest and concern regarding the environmental impact of inhaled therapies and the increasingly available data from carbon footprint assessments may be considered when making treatment decisions. Further data on the wider environmental impacts of inhalers could also be considered as they become available, to encompass a broader range of environmental impacts beyond carbon footprint (*e.g.* freshwater/marine eutrophication or nonrenewable resource consumption). For example, while pMDIs also contain plastic and aluminium, the quantity of these materials in at least one DPI (Diskus) has been estimated to lead to worsened outcomes for some environmental impacts *versus* select pMDIs (*e.g.* metal depletion and terrestrial acidification) [10]. However, we anticipate that the use of newer, refillable DPIs will decrease this effect, due to decreased raw material depletion [10, 37]. Complete data on one such device, the Breezhaler DPI, has recently been released, showing the relative contributions of each life cycle stage to six environmental impact categories (climate change, ecotoxicity, freshwater use, resource depletion, ozone depletion and acidification potential) [37].

Following efficacy and safety considerations, comprehensive data on the carbon footprint of inhaled therapies will enable patients and their carers to make informed decisions about their inhaled treatment. Pharmaceutical companies should be considering these issues in their strategic forward planning for novel developments in inhaled therapy.

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