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Early View

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The environmental impact of inhaled therapy: making informed treatment choices

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Short summary

There is increasing interest regarding the carbon footprint of inhaled therapies; whilst efficacy, safety and patient preference should be prioritised, the increasingly available carbon footprint data may be factored into treatment decision making.

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 CO_2 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 will 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, nitrous oxide and methane) 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, design, production, transportation, utilisation and end of life/disposal) [2]. This is often stated in "CO_2 equivalents" or "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 greenhouse gases) [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, though 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* 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; carbon dioxide 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 to existing propellants [10, 17]. These HFCs (HFC-134a, -227ea, and -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 ~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 approximately 18,000 kt CO_2 eq in 2018, which was approximately 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 two kilometres 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 United Kingdom 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 (BTS) 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 have examined the currently available carbon footprint data for inhaled therapies and assessed potential implications for treatment decision making and industry

initiatives. The aim of this 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, or 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, for example 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 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.

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

	Carbon Trust, for GlaxoSmithKline PLC 2014 Product Carbon Footprint Certification Summary Report (2014 Carbon Trust) [26]	**Jeswani & Azapagic 2019** Academic appraisal: Life cycle environmental impacts of inhalers [10]	**Panigone *et al.* 2020** Environmental impact of inhalers for respiratory diseases: decreasing carbon footprint while preserving patient-tailored treatment [27]	**Hänsel *et al.* 2019** Reduced Environmental Impact of the Reusable Respimat® Soft Mist™ Inhaler Compared with Pressurised Metered-Dose Inhalers [28]	**Carbon Footprint Ltd., for Orion Pharma 2020** Carbon Life Cycle Assessment Report for Orion Corporation, Orion Pharma [29, 30]	**Aumônier *et al.* 2020** Carbon footprint assessment of Breezhaler® dry powder inhaler [31]
Inhaler and drug combination(s) studied (pack size)	- SAL/FP 25/250 µg pMDI (30-day) - FF/VI 92/22 µg DPI (Relvar Ellipta; 30-day) - SAL/FP 50/500 µg Accuhaler DPI (Diskus; 30-day)	Inhaler devices only, API not considered: - HFC-134a pMDI (100 dose/200 act) - HFC-227ea pMDI (60 dose/120 act) - HFC-152a pMDI (100 dose/200 act) - DPI (Diskus) (60 dose)	- FORM/BDP 6/100 µg pMDI (120 dose)* - FORM/BDP NEXThaler 6/100 µg (120 dose)*	- TIO Respimat® SMI (both disposable and reusable; 60 act/month) - IB/FEN Respimat® SMI (120 act/month) - IB/FEN HFC pMDI (200 act/ month) - IB HFC pMDI (200 act/ month)	Easyhaler® DPI: - BUD/FORM 160/4.5 µg (120 doses) - SAL/FP 50/250 µg (60 doses) - SALB 100 µg (200 doses) - FORM 12 µg (120 doses)	Breezhaler® DPI: - IND/GLY/MF (30-dose) + sensor - IND/GLY/MF (30-dose) - IND/GLY/MF (90-dose) - IND/MF (30-dose)
Method and standard(s) applied	PAS2050/GHG Protocol Product Standard Sector Guidance – Carbon Trust Footprint Expert Tool	ISO 14040 & ISO14044 (multiple environmental impacts appraised) [32, 33]	ISO14067/GHG Protocol Product Standard Sector Guidance [2, 34]	Intergovernmental Panel on Climate Change Fifth Assessment Report on Climate Change, GHG Protocol Product Life Cycle Accounting and	Analysis conducted by Carbon Footprint Ltd in accordance with ISO14067: 2018 standard [2] (Multiple environmental impacts appraised)	The streamlined LCA was completed in accordance with the Greenhouse Protocol Product Accounting and Reporting Standard using Sector

				Reporting Standard and standard sector guidance [25, 34, 35]		Guidance for Pharmaceuticals and Medical Devices [25]
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 was conducted by ISO14001:2015 and 9001:2015 certified Carbon Footprint Ltd	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	✓	✗	✓	✓	✓	✓
Production of final product	✓	✓	✓	✓	✓	✓
Packaging	✓	✗	✓	✓	✓	✓
Distribution and storage	✓	✓	✓	✓	✓	✓
Pharmacy/retail	✗	✗	✗	Not stated	Not stated	✗
Patient travel	Not stated	✗	Not stated	Not stated	Not stated	✗
Patient use	✓	✓	✓	✓	Not stated	✗

End-of-life disposal	✓	✓	✓	✓	✓	✓

act: actuations; API: active pharmaceutical ingredient; BDP: beclometasone dipropionate; BUD: budesonide; DPI: dry powder inhaler; FEN: fenoterol hydrobromide; FF: fluticasone furoate; FORM: formoterol; FP: fluticasone propionate; GHG: greenhouse gas; GLY: glycopyrronium bromide; HFC: hydrofluorocarbon; IB: ipratropium bromide; IND: indacaterol acetate; LCA: life cycle assessment; MF: mometasone furoate; PAS: publicly available specification; pMDI: pressurised metered dose inhaler; SAL: salmeterol; SALB: salbutamol; SMI: soft mist inhaler; TIO: tiotropium bromide; VI: vilanterol;

*: other drug/device combinations investigated in this study have not been discussed here.

TABLE 2. Summary of results: studies investigating the carbon footprints of respiratory inhalers

Publication	**Carbon Trust, for GlaxoSmithKline PLC 2014** Product Carbon Footprint Certification Summary Report (2014 Carbon Trust) [26]	**Jeswani & Azapagic 2019** Academic appraisal: Life cycle environmental impacts of inhalers [10]*	**Panigone *et al.* 2020** Environmental impact of inhalers for respiratory diseases: decreasing carbon footprint while preserving patient-tailored treatment [27]	**Hänsel *et al.* 2019** Reduced Environmental Impact of the Reusable Respimat® Soft Mist™ Inhaler Compared with Pressurised Metered-Dose Inhalers [28]	**Carbon Footprint Ltd., for Orion Pharma 2020** Carbon Life Cycle Assessment Report for Orion Corporation, Orion Pharma [29, 30]	**Aumônier *et al.* 2020** Carbon footprint assessment of Breezhaler® dry powder inhaler [31]
Inhaler and drug combination(s) studied (pack size)	Full life cycle appraised: - SAL/FP 25/250 µg pMDI (30-day) - FF/VI 92/22 µg DPI (Relvar Ellipta; 30-day) - SAL/FP 50/500 µg Accuhaler DPI (Diskus; 30-day)	Inhaler devices only, API not considered: - HFC-134a pMDI (100 dose/200 act) - HFC-227ea pMDI (60 dose/120 act) - HFC-152a pMDI (100 dose/200 act) - DPI (Diskus) (60 dose)	Full life cycle appraised: - FORM/BDP 6/100 µg pMDI (120 dose)* - FORM/BDP NEXThaler 6/100 µg (120 dose)*	Full life cycle appraised: - TIO Respimat® SMI (disposable; 60 act/month) - IB/FEN Respimat® SMI (120 act/month) - IB/FEN HFC pMDI (200 act/ month) - IB HFC pMDI (200 act/ month)	Full life cycle appraised: Easyhaler® DPI: - BUD/FORM 160/4.5 µg (120 doses) - SAL/FP 50/250 µg (60 doses) - SALB 100 µg (200 doses) - FORM 12 µg (120 doses)	Full life cycle appraised: Breezhaler® DPI: - IND/GLY/MF (30-dose) + sensor - IND/GLY/MF (30-dose) - IND/GLY/MF (90-dose) - IND/MF (30-dose)†
Carbon footprint, kg CO_2 eq/month	SAL/FP 25/250 µg pMDI = 20.370 FF/VI 92/22 µg DPI = 0.765 SAL/FP 50/500 µg	HFC-134a pMDI = 31.56‡ HFC-227ea pMDI = 83.64‡ HFC-152a pMDI = 2.4‡	FORM/BDP 6/100 µg pMDI = 11.33‡ FORM/BDP NEXThaler 6/100 µg = 0.916‡	TIO Respimat® SMI (disposable) = 0.775 IB/FEN Respimat® SMI = 0.784 IB/FEN HFC pMDI	Easyhaler® DPI: - BUD/FORM 160/4.5 µg = 0.514 - SAL/FP 50/250 µg = 0.602 - SALB 100 µg = 0.664 for	Breezhaler® DPI: - IND/GLY/MF (30-dose) + sensor = 0.481 - IND/GLY/MF (30-dose) = 0.359

	Accuhaler (Diskus) DPI = 1.250	DPI (Diskus) = 1.08‡		= 16.484 IB HFC pMDI = 14.585	total life cycle¶ - FORM 12 µg = 0.287§	- IND/GLY/MF (90-dose) = 0.184
Main contributor(s) to total carbon footprint	SAL/FP 25/250 µg pMDI = propellant (74% of CF [56% during use, 18% at end-of-life disposal]) 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 (Diskus) DPI = API and device production (77% of total carbon footprint [48% API production, 29% device production])	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 6/100 µg pMDI = propellant (92.5% of total carbon footprint [70.2% during use, 22.3% at end-of-life disposal]) FORM/BDP NEXThaler 6/100 µg = manufacture of the device and packaging (57.9% of the total carbon footprint [32.2% device packaging, 25.7% energy and water consumption during manufacture])	TIO Respimat® SMI (disposable) and IB/FEN Respimat® SMI = manufacture of the 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 the 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

act: actuations; API: active pharmaceutical ingredient; BDP: beclometasone dipropionate; BUD: budesonide; CF: carbon footprint; DPI: dry powder inhaler; FEN: fenoterol hydrobromide; FF: fluticasone furoate; FORM: formoterol; FP: fluticasone propionate; GLY: glycopyrronium

bromide; HFC: hydrofluorocarbon; IB: ipratropium bromide; IND: indacaterol acetate; MF: mometasone furoate; pMDI: pressurised metered dose inhaler; SAL: salmeterol; SALB: salbutamol; SMI: soft mist inhaler; TIO: tiotropium bromide; VI: vilanterol.

*: 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/month (two actuations twice daily for 30 days); §: value assumes maintenance use: for more severe disease, dose and emissions are doubled; ¶: 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; ||: the main contributor(s) to the carbon footprint were not specified per product in this reference

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 ~~of~~ the active pharmaceutical ingredients (API). In contrast, for SAL/FP 25/250 µg HFC-134a pMDI, 74% of the much larger carbon footprint resulted from the propellant alone.

Jeswani & Azapagic compared a DPI (Diskus) *versus* HFC pMDIs containing three different propellants (HFC-134a, HFC-227ea and HFC-152a) [10]. This assessment included the production of the device and propellants (for pMDIs), inhaler use, and end-of-life disposal; APIs were not considered [10]. Jeswani & Azapagic estimated that if all prescribed pMDIs in the United Kingdom (UK) were replaced by currently available DPIs (assuming 9 g CO_2 eq/dose), the estimated reduction in carbon footprint would be 96%. The theoretical future replacement of all HFC-227ea (697g CO_2 eq/dose) and HFC-134a (263g CO_2 eq/dose) pMDIs by those containing HFC-152a (assuming 20 g CO_2 eq/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.* assessed the carbon footprint of combination formoterol/beclometasone dipropionate (FORM/BDP) 6/100 µg in the NEXThaler DPI *versus* a HFC-134a pMDI formulation [27]. Based on a month's treatment, the DPI had a carbon footprint of 0.916 kg CO_2 eq, *versus* 11.33 kg CO_2 eq for the pMDI, meaning one months' pMDI use was approximately equivalent to a year of DPI use (table 2, 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 soft mist versus pMDI inhalers

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*. carried out a study comparing the carbon footprints 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) [28] (figure 2c, 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 this study [28]. Switching from an HFC pMDI to a disposable SMI would result in an approximate 95% reduction in life cycle carbon footprint, a similar reduction to a switch to a DPI [10, 28]. Compared with the disposable device over one month, use of the reusable TIO Respimat® over three 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® products (DPI) were assessed in a cradle-to-grave study by Carbon Footprint Ltd. [29, 30]. Table 2 shows the carbon emissions, per month, for the maintenance products included in this 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].

A life-cycle assessment, 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, MF, and glycopyrronium bromide (GLY) 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 this 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 fluticasone propionate/formoterol pMDI is known to use 11 g of HFC-227ea propellant [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 *et al.* 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 [10]. 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, *et al.* 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/Conclusions

Greenhouse gases 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), amongst 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 greenhouse gases, 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]. Further, the carbon footprint of different HFC-134a salbutamol pMDIs 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 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 a HFC-134a pMDI and just 1.3% of a HFC-227ea pMDI (without consideration of 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]. Further, Janson *et al*. 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 of CO_2 eq [44].

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 propellant could result in an approximate 10- to 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 (for example, 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 BUD/FORM 200/6 µg DPI led to a reduction in overall GHG emissions of around 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 around 60% and 32%, respectively (also largely due to reductions in hospital admissions and associated travel). In the real-world Salford Lung Study for 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 one 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 the Salford Lung Study had a significant saving in their carbon footprint compared to 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 FEV_1 following a 50 µg or

400 µg dose of salbutamol is similar [56], suggesting that a sub-optimal 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 multi-dose 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 (budesonide 200 µg and fluticasone propionate 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 non-medical 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], though it is not yet commercialised in inhalers and the potential future market and cost implications for HFC-152a chemical from non-medical applications (for example, in 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 have 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; the 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; 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 it becomes available, to encompass a broader range of environmental impacts beyond carbon footprint (*e.g.* freshwater/marine eutrophication or non-renewable 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 lifecycle stage to six environmental impact categories (global warming potential; acidification; ozone depletion; use of resource, minerals, and metals; eco-toxicity; and freshwater use) [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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Conflicts of interest

Prof Ashley Woodcock is Co-chair of the Montreal Protocol Technology and Economic Assessment Panel, and member of the Medical and Chemical Technical Options Committee have received compensation for consulting activities from GlaxoSmithKline, Novartis, and Sandoz UK; compensation for speaker activities from Novartis, GlaxoSmithKline, and Teva. Dr Kai-Michael Beeh and/or the institution he represents have in the past 5 years received compensation for services on advisory boards or consulting activities from AstraZeneca, Berlin Chemie, Boehringer, Chiesi, Elpen, GSK, Mundipharma, Novartis, Pohl Boskamp, Sanofi, and Teva; compensation for speaker activities in scientific meetings supported by AstraZeneca, Berlin Chemie, Boehringer, Chiesi, Elpen, ERT, GSK, Novartis, Pfizer, Pohl Boskamp, Sanofi and Teva; compensation for design and performance of clinical trials from AstraZeneca, Boehringer, GSK, Novartis, Parexel, Pearl Therapeutics, Teva and, sterna. Prof Hironori Sagara receives compensation for speaker activities in lectures supported by AstraZeneca, GSK, Novartis, and Sanofi.

Simon Aumônier is employed by ERM, a global sustainability consulting company that undertakes engagements with a wide range of public sector companies, including many in the healthcare sector and including Novartis.

Prof Emmanuel Addo-Yobo is employed by the Kwame Nkrumah University of Science and Technology, in the Department of Child Health, School of Medicine and Dentistry, and is Honorary Consultant Paediatrician at the Komfo Anokye Teaching Hospital, Kumasi, Ghana with special interest in paediatric asthma and respiratory care and research; has received compensation as resource person for asthma educational activities supported by AstraZeneca in Ghana.

Prof Javaid Khan and/or the institution he represents have received research grant from NIHR UK for work on Smokeless Tobacco and Campaign for Tobacco Free Kids for a pilot study on looking at smoking policies at Restaurants in Karachi, and is a member of the Medical and Chemical Technical Options Committee.

Jørgen Vestbo has received honoraria for presenting and/or advising from AstraZeneca, Boehringer-Ingelheim, Chiesi, GSK, Novartis and Teva.

Helen Tope is employed by Planet Futures, a consulting business providing services to government, industry and other non-governmental organisations on climate change, ozone-depleting substances, and other environmental issues. As an independent expert, she co-chairs the Medical and Chemicals Technical Options Committee, which provides technical and economic advice, including on inhalers, to the Montreal Protocol. The views expressed herein are those of the co-authors and do not represent those of the Medical and Chemicals Technical Options Committee.

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Figure legends

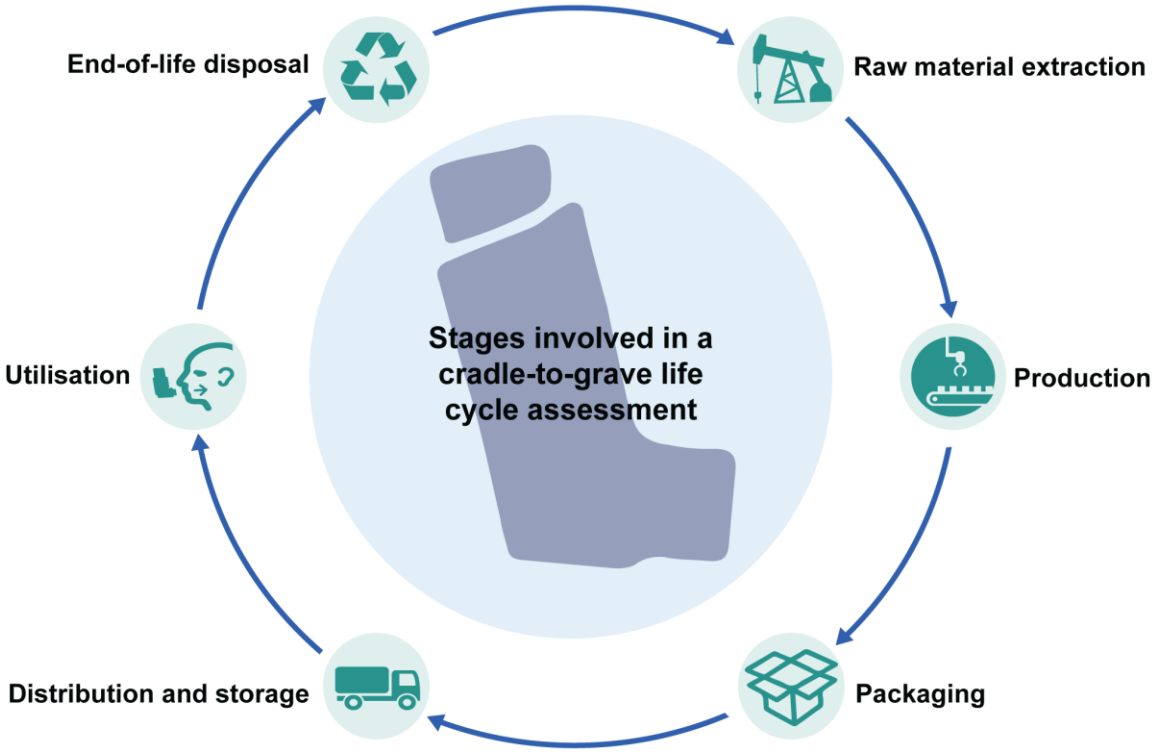


FIGURE 1. The stages involved in a cradle-to-grave life cycle assessment [2].

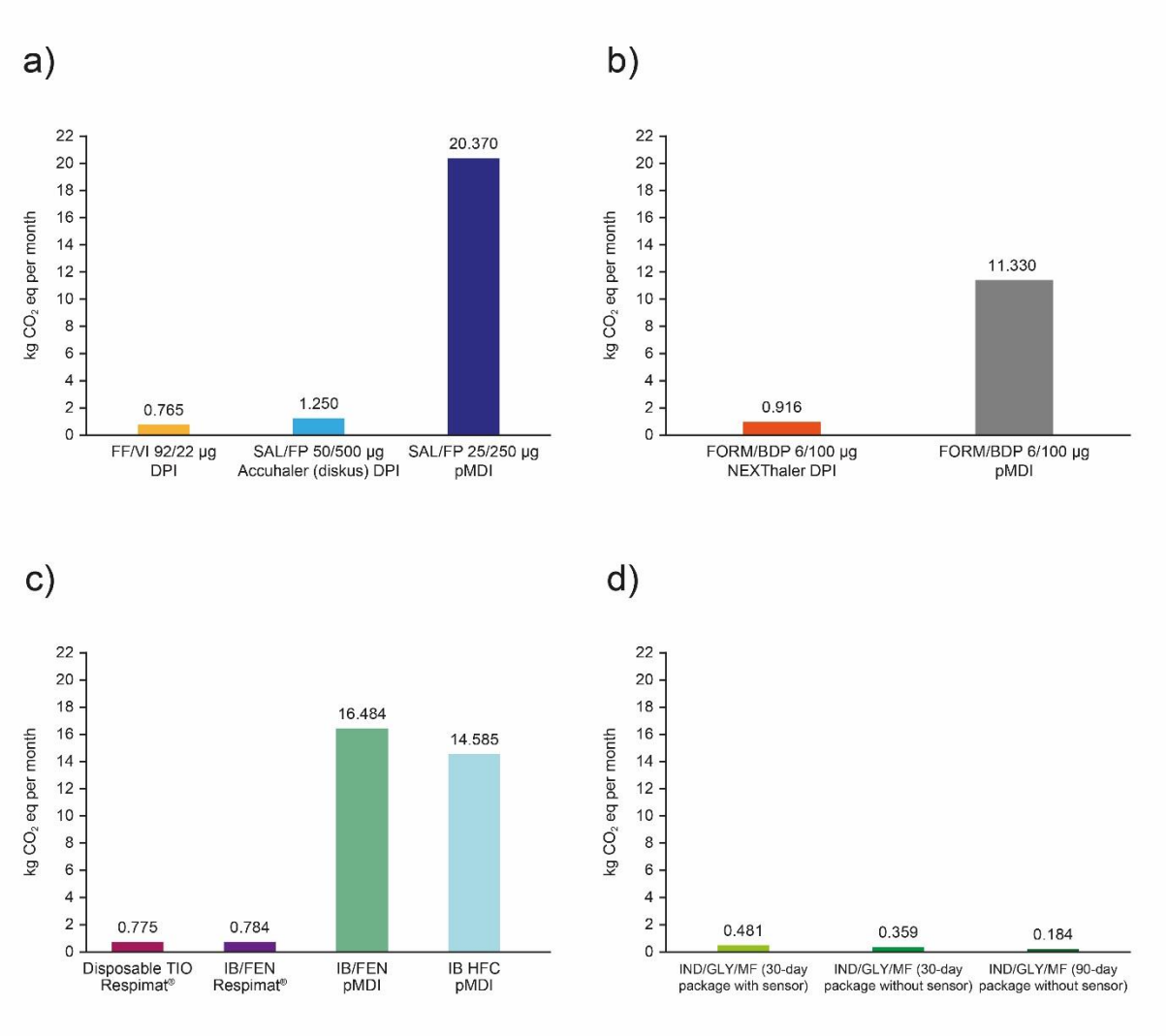
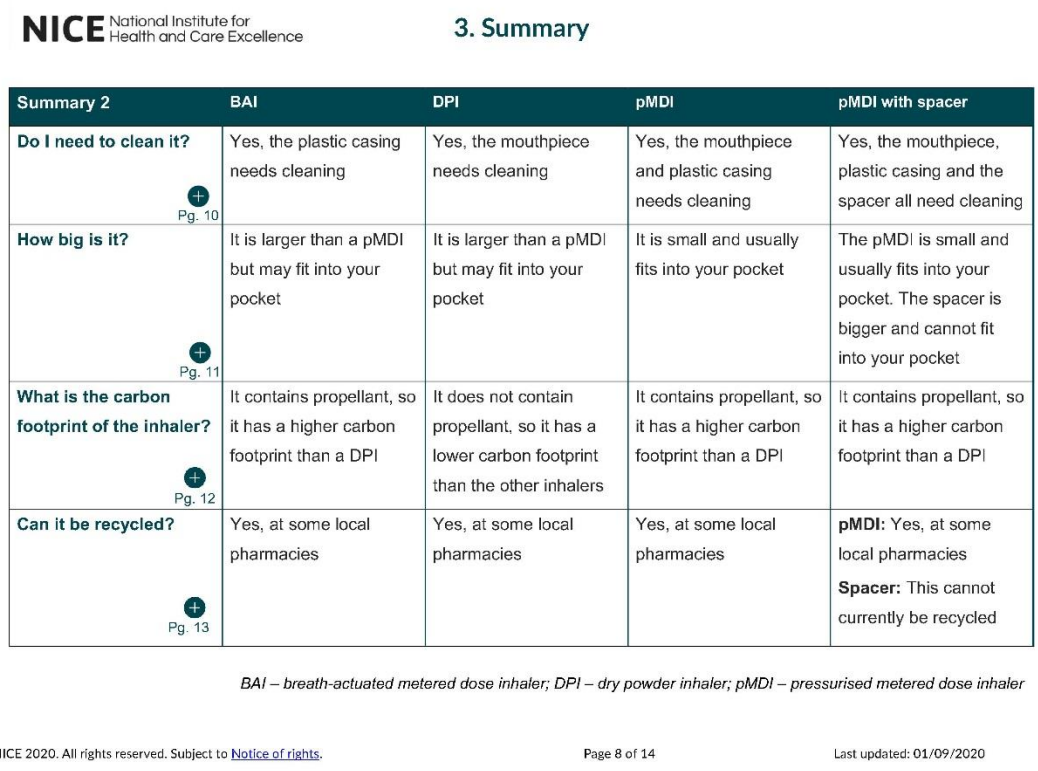


FIGURE 2. Carbon footprint per month for a) SAL/FP 25/250 µg pMDI, FF/VI 92/22 µg DPI and SAL/FP 50/500 µg DPI (API included) [26]; b) FORM/BDP 6/100 µg as NEXThaler DPI *versus* pMDI (API included) [27]; c) Disposable TIO Respimat® SMI, IB/FEN Respimat® SMI, IB/FEN HFC pMDI and IB HFC pMDI (API included) [28]; d) Breezhaler® IND/GLY/MF devices per month (API included) [31].

API: active pharmaceutical ingredient; BDP: beclometasone dipropionate; CO_2 eq: carbon dioxide equivalent; DPI: dry powder inhaler; FEN: fenoterol hydrobromide; FF: fluticasone furoate; FORM: Formoterol; FP: fluticasone propionate; GLY: glycopyrronium bromide; HFC: hydrofluorocarbon; IB: ipratropium bromide; IND: indacaterol acetate; MF: mometasone

furoate; pMDI: pressurized metered dose inhaler; SAL: salmeterol xinafoate; TIO: tiotropium; VI: vilanterol.



NICE National Institute for Health and Care Excellence

3. Summary

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

BAI – breath-actuated metered dose inhaler; DPI – dry powder inhaler; pMDI – pressurised metered dose inhaler

FIGURE 3. The carbon footprint of inhalers referenced in the National Institute for Health and Care Excellence (NICE) patient decision aid for inhalers for asthma [60].