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Review

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MDPI

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Carbon Footprints and Life Cycle Assessments of Inhalers: A Review of Published Evidence

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Abstract: Respiratory inhalers have a substantial impact on the carbon footprint of the healthcare sector. Environmental factors, including carbon footprints, are gaining importance in choosing inhalers once medical considerations have been addressed. This paper provides a review of the carbon footprint (CFP) and life cycle assessment (LCA) environmental profile of dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs). Despite methodological challenges, our analysis reveals that the CFP varies between DPIs ranging from 359 gCO_2e per inhaler (Enerzair Breezhaler® DPI without digital companion 30-day pack) to 1250 gCO_2e per inhaler (Seretide Accuhaler® 50/500) and from 6.13 gCO_2e per dose (Enerzair Breezhaler® without digital companion 90-day pack) to 27 gCO_2e per dose (Relvar Elipta 92/22). The breakdown of inhaler CFP by life cycle stage reveals that, although the use and end-of-life stages together contribute to most of the CFP of the MDIs, the largest contributions to the CFP of the DPI/SMI are made by the API and manufacturing stages of the life cycle. Although from a climate perspective our review aligns with the findings of Jeswani and Azapagic that DPIs have a lower CFP than pMDIs, we conclude that the performance against other environment impact categories depends on the design, choice of material and manufacturing process of the DPIs. The challenge of comparing the CFP of different inhalers can be made easier by the standardization of study boundaries and methods.

Keywords: life cycle assessment; environmental impact; cradle-to-grave; carbon footprint

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1. Introduction

The delivery of drugs through inhalation is the cornerstone of respiratory disease management. The inhaled route offers drug delivery directly to the lungs and allows the use of smaller doses, and thus, it has a better efficacy-to-safety ratio compared with systemic therapy. The respiratory inhalers used today include nebulizers, metered-dose inhalers (MDIs), pressurized MDIs (pMDIs), dry powder inhalers (DPIs) and soft mist inhalers (SMI). MDIs or pMDIs are the most commonly used inhaler devices in the UK as well as in other markets worldwide [1].

There is a growing awareness among healthcare professionals and patients of the environmental impact contributions of respiratory inhalers due to the presence of propellants. As a result of the global warming potential (GWP) of the propellants (e.g., HFC 134a [GWP of 1300] and HFC 227a [GWP of 3350]) and the frequent use of inhalers, MDIs make a significant contribution to the overall carbon footprint (CFP) of healthcare [2]. It has been estimated that MDIs are responsible for 3.1% of the total CFP of the National Health Service (NHS) in the UK [3]. Currently, DPIs and SMIs are available as inhaler devices that use no propellant gas and hence have a significantly reduced CFP [4]. The Montreal Protocol Medical and Chemical Technical Options Committee has estimated that the CFP of pMDIs is approximately 13-fold higher when compared to DPIs (1.5–6 $kgCO_2e$ and 20–80 $kgCO_2e$ for 200 actuations of DPIs and pMDIs, respectively) [5].

Although the clinical condition of the patient takes top priority when deciding the choice of inhaler and medication, environmental factors are gaining importance in decision making once medical considerations have been addressed. Good-quality data comparing the environmental impact of different inhalers can be useful when choosing the inhaler that has the smallest environmental impact. The aim of this article is to review the existing scientific literature with regard to life cycle assessment (LCA) and CFP for DPIs and pMDIs. We reviewed, reported and calculated inhaler CFP data, as well as the breakdown of CFP data by life cycle stage and the life cycle impact assessment of DPIs and MDIs.

2. Methods

2.1. Literature Search

A Google Scholar literature search was conducted to identify studies evaluating the environmental impact of different types of inhaler devices throughout their life cycles. The literature search was conducted to evaluate evidence from such studies published up until June 2021. Searches were made with the keywords (or slight variations thereof) "DPI", "dry powder inhaler", "MDI", "metered-dose inhaler", "inhaler", "carbon footprint", "LCA", "lifecycle" and "assessment". The search results were further screened to include only articles which reported the CFP of inhalers or the results of the LCA of inhalers. We included seven published papers that met these criteria [6–12].

A footprint for a relevant functional unit (per dose, per actuation and per inhaler) is reported where it is included in the study, or where this footprint can be calculated from the study or other available information. In some cases, data from Janson et al. [6], the Carbon Trust [11] and Wilkinson et al. [7] were combined in these calculations. For the comparison of life cycle impact assessments, the results are presented as a percentage of the highest impact across the full range of inhalers.

2.2. Methodological Analysis of Sources

There is some variability in the methods or standards adopted by the various studies, where these have been referenced. Some studies have been independently verified as conformant with the relevant standard, for example, the Greenhouse Gas (GHG) Protocol [13]. A summary of key criteria is presented in Table 1.

3. Results

3.1. Reported and Calculated Inhaler Carbon Footprint Data

Table 2 lists the name and type of the device, the active pharmaceutical ingredient (API) delivered and the propellant used where the study refers to an MDI device, together with the number of actuations per dose and the number of actuations per inhaler, where these are provided. It then presents the CFP according to three separate (but associated) functional units: per dose, per actuation and per inhaler. Where the CFP is not available or cannot be calculated, the relevant cell(s) in the table is filled with a dash (thus '-').

3.2. Carbon Footprint of MDIs and DPIs

The CFP per inhaler of the respiratory inhalers evaluated ranged from 359 to 36,500 gCO_2e. Whereas the MDIs evaluated had an average CFP per inhaler of approximately 18,000 gCO_2e, the DPIs evaluated have an average CFP per inhaler of approximately 700 gCO_2e. Of all the devices compared, the highest CFP per actuation and per inhaler (295 gCO_2e per actuation and 36,500 gCO_2e per inhaler, respectively) is for generic or unspecified MDI devices, which use HFA227ea, which has a much higher GWP than HFA13a. Among the inhalers identified by brand name, Seretide Evohaler® 25/250 (339.46 gCO_2e per dose and 169.73 gCO_2e per actuation) and the Ventolin Evohaler® (28,000 gCO_2e per inhaler) have the highest CFPs. These devices use HFA134 as a propellant (Table 2).

Table 1. Methodological analysis of sources.

	Janson et al. [6]	**Carbon Trust [11]**	**Wilkinson et al. [7]**	**Panigone et al. [8]**	**Novartis [12,14]**	**Hänsel et al. [9]**	**Lehtimaki L [10]**
Year	**2019**	**2014**	**2018**	**2020**	**2020**	**2019**	**2019**
Method and standards applied	GSK calculated. Method not stated.	PAS2050/GHG Protocol Product Standard Sector Guidance/Carbon Trust Footprint Expert Tool	Indicative CFP quoted from a range of sources and methods are not stated in all cases	ISO14067/GHG Protocol Product Standard Sector Guidance	Streamlined LCA to appraise CFP Aligned with GHG Protocol Product Standard Sector Guidance	GHG Protocol Product Standard Sector Guidance	Analyses were performed in accordance with ISO 14040 and ISO 14044. Multiple environmental impacts were appraised.
Assurance/verification	Individual product CFP verified by Carbon Trust	Individual product CFP verified by Carbon Trust as conformant with the above standards. Review report published.	Review includes some independently verified studies, but also some patent data and other assessments published by the manufacturer.	Third party. The calculation tool/procedure (Carbon Footprint Systematic Approach [CF-SA]) is stated as being certified. Product footprints reported as being verified to the above standards. However, the text suggests that a "system" has been developed and certified to avoid the need for this for individual footprints. Tool verification is no guarantee of conformity for product assessments.	Critically reviewed	No details given other than checking and resolving data gaps internally.	Analysis is stated as having been verified by Carbon Footprint Ltd.
Functional unit	Per inhaler, per year	Per dose, per actuation and per inhaler	Per inhaler, per actuation	Per actuation	Per dose, per inhaler	Per month	Per inhaler
Life cycle boundary full = cradle-to-grave, from extraction of resources from ground, through API, excipient, propellant and device manufacture to pharmacy, patient use and disposal at end-of-life.	Full life cycle	Full life cycle appraised. Pharmacy/retail stage excluded as not material. Primary data collected from suppliers for API (2013) and device manufacture (2010/11). Primary data for GSK operations. Not reported whether patient travel is included (the standard states patient travel should be included—results suggest excluded).	Life cycle boundaries are not clearly stated in the review. The focus is on the contribution of propellant to the footprint of the inhaler, and other contributions appear to be excluded in some instances. As a result, some MDI footprints quoted in this review may be underestimated.	Full life cycle appraised. Pharmacy/retail stage excluded. Secondary data are assumed to be used for API and device component manufacture (not stated). Primary data for Chiesi operations is assumed, given requirements of standard. Not reported whether patient travel is included (the standard states patient travel should be included—results suggest excluded).	Full life cycle appraised using secondary data/estimates. Pharmacy/retail and patient travel excluded.	Full life cycle including material acquisition and pre-processing, production, distribution, use and end-of-life. Primary data collected from the supply chain, with key assumptions for distribution and end-of-life. Patient travel is excluded.	Cradle-to-grave assessment, including API, packaging, distribution, disposal, etc.Data collected from Orion, suppliers and reference data bases in 2019.Not stated if patient travel is included (standard states patient travel should be included).

API, active pharmaceutical ingredient; CFP, carbon footprint; GHG, greenhouse gas; MDI, metered-dose inhaler.

Table 2. Reported and calculated inhaler carbon footprint data.

Device Name	API	Device Type	Propellant	Actuations per Inhaler	Actuations per Dose	CFP per Dose (/gCO_2e)	CFP per Actuation (/gCO_2e)	CFP per Inhaler Pack (/gCO_2e)
Atrovent HFA [9]	Ipratropium bromide	MDI	HFA 134a	200	-	-	72.93	14,585
Berodual HFA [9]	Ipatropium bromide/ fenoterol hydrobromide	MDI	HFA 134a	200	-	-	82.42	16,484
Clenil Modulite 100 [8]	Beclometasone dipropionate	MDI	HFA 134a	200	-	166.20	83.10	16,620
Clenil Modulite 200 [8]	Beclometasone dipropionate	MDI	HFA 134a	200	-	163.92	81.96	16,392
Foster 100/6 [8]	Beclometasone dipropionate/ formoterol	MDI	HFA 134a	120	2	188.84	94.42	11,330
Foster 200/6 [8]	Beclometasone dipropionate/ formoterol	MDI	HFA 134a	120	2	237.12	118.56	14,227
Generic (i.e., Atrovent) [7]	Generic SAMA	MDI	HFA 134a	200	-	-	71.50	14,300
Generic (i.e., Clenil) [7]	Generic ICS	MDI	HFA 134a	200	-	-	101.75	20,350 *
Generic (i.e., Flutiform) [7]	Generic ICS/LABA	MDI	HFA 227ea	120	-	-	295	36,500 *
Generic (i.e., Foster) [7]	Generic ICS/LABA	MDI	HFA 134a	120	-	-	163.75	19,650 *
Generic (i.e., Salamol) [7]	Generic small volume SABA	MDI	HFA 134a	200	2	98.70	49.35	9870 *
Generic (i.e., Salmerol) [7]	Generic LABA	MDI	HFA 134a	120	-	-	130	15,600
Generic (i.e., Ventolin) [7]	Generic large volume SABA	MDI	HFA 134a	200	2	252.6	126.30	25,260 *
Seretide Evohaler 25/250 [6]	Fluticasone propionate/salmeterol	MDI	HFA 134a	120	2	317	158	19,000
Seretide Evohaler 25/250 (2014 data) [11]	Fluticasone propionate/salmeterol	MDI	HFA 134a	120	2	339.46	169.73	20,370
Trimbow [8]	Beclometasone dipropionate/ formoterol/ glycopyrronium bromide	MDI	HFA 134a	120	-	-	118.99	14,279
Ventolin Evohaler 100 [6]	Salbutamol	MDI	HFA 134a	200	-	-	140	28,000
Breezhaler® 30 day without digital companion, used in Germany ** [12,14]	Indacaterol acetate/mometasone furoate	DPI	None	30	1	12.80	12.80	384
Breezhaler® 30 day without digital companion, used in Germany ** [12,14]	Indacaterol acetate/ mometasone furoate/ glycopyrronium bromide	DPI	None	30	1	11.96	11.96	359
Breezhaler® 30 day with digital companion, used in Germany ** [12,14]	Indacaterol acetate/mometasone furoate/glycopyrronium bromide	DPI	None	30	1	16.03	16.03	481
Breezhaler® without digital companion (90 day), used in Germany ** [12,14]	Indacaterol acetate/mometasone furoate/glycopyrronium bromide	DPI	None	90	1	6.13	6.13	-
Easyhaler [10]	Average of salbutamol, formoterol, salmeterol-fluticasone and budesonide-formoterol	DPI	None	-	-	-	-	588.50

Table 2. *Cont.*

Device Name	API	Device Type	Propellant	Actuations per Inhaler	Actuations per Dose	CFP per Dose (/gCO_2e)	CFP per Actuation (/gCO_2e)	CFP per Inhaler Pack (/gCO_2e)
Foster NEXThaler 100/6 [8]	Beclometasone dipropionate/formoterol	DPI	None	120	1	7.63	7.63	916
Foster NEXThaler 200/6 [8]	Beclometasone dipropionate/formoterol	DPI	None	120	1	7.64	7.64	917
Relvar Elipta 92/22 [6]	Fluticasone furoate/vilanterol	DPI	None	30	1	27	27	800
Relvar Elipta 92/22 (2014 data) [11]	Fluticasone furoate/vilanterol	DPI	None	30	1	25.50	25.50	764.66
Seretide Accuhaler 50/500 [6]	Fluticasone furoate/salmeterol	DPI	None	60	1	15	15	900
Seretide Accuhaler 50/500 (2014 data) [11]	Fluticasone furoate/salmeterol	DPI	None	60	1	20.86	20.86	1250
Ventolin Accuhaler 200 [6]	Salbutamol	DPI	None	-	-	-	-	600
Berodual Respimat [9]	Ipatropium bromide/ fenoterol hydrobromide	SMI	None	120	1	6.46	6.46	775
Spiriva Respimat [9]	Tiotropium bromide	SMI	None	60	2	25.83	12.92	775
Spiriva Respimat (3-month pack) [9]	Tiotropium bromide	SMI	None	-	2	11.33	5.67	-
Spiriva Respimat (6-month pack) [9]	Tiotropium bromide	SMI	None	-	2	7.67	3.83	-

* Midpoint of quoted range; ** The digital companion consists of a sensor and an app, which is designed to provide inhalation confirmation, medication reminders and access to objective data to better support therapeutic decisions; DPI, dry powder inhaler; HFA, hydrofluoroalkane; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; MDI, metered-dose inhaler; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist; SMI, soft mist inhalers. Grey background color indicate the lowest CFP.

At the other end of the range, DPI/SMI devices have maximum CFPs between 20 and 40 times less than MDI on a per-dose and per-actuation basis, depending on whether older sources and unnamed devices were included. The highest CFP for a DPI/SMI device per dose and per actuation is 27 gCO_2e (for the Relvar Elipta® 92/22 device). The highest CFP for a DPI/SMI device per inhaler, which is for the Seretide Accuhaler® 50/500, is 1250 gCO_2e. Note that this source used 2014 data. The Foster NEXThaler® 200/6 has the next highest footprint of 917 gCO_2e per inhaler (Table 2).

Breezhaler® DPIs have the lowest CFP for each functional unit per dose, per actuation and per inhaler (devices with the lowest CFP are shaded in grey in Table 2). The Breezhaler® 90-day pack without a digital companion, using the indacaterol acetate, mometasone furoate and glycopyrronium bromide (IND/GLY/MF) API combination, has the lowest CFP per dose and per actuation. The Breezhaler® 30-day pack without a digital companion, using the IND/GLY/MF API combination, has the lowest CFP per inhaler.

3.3. Breakdown of Reported and Calculated Inhaler Carbon Footprint Data by Life Cycle Stage

Table 3 presents a breakdown of the CFP per inhaler according to contribution by life cycle stage: API, manufacture, distribution, use and end-of-life. A breakdown of the CFPs is not available in all cases, and, in some instances, the API is included in the manufacture stage, as indicated in the table with cell input "Incl. in mnfctr". Figure 1 is a graphic representation of the breakdown of the footprint by life cycle stage, where this granularity is available at the source.

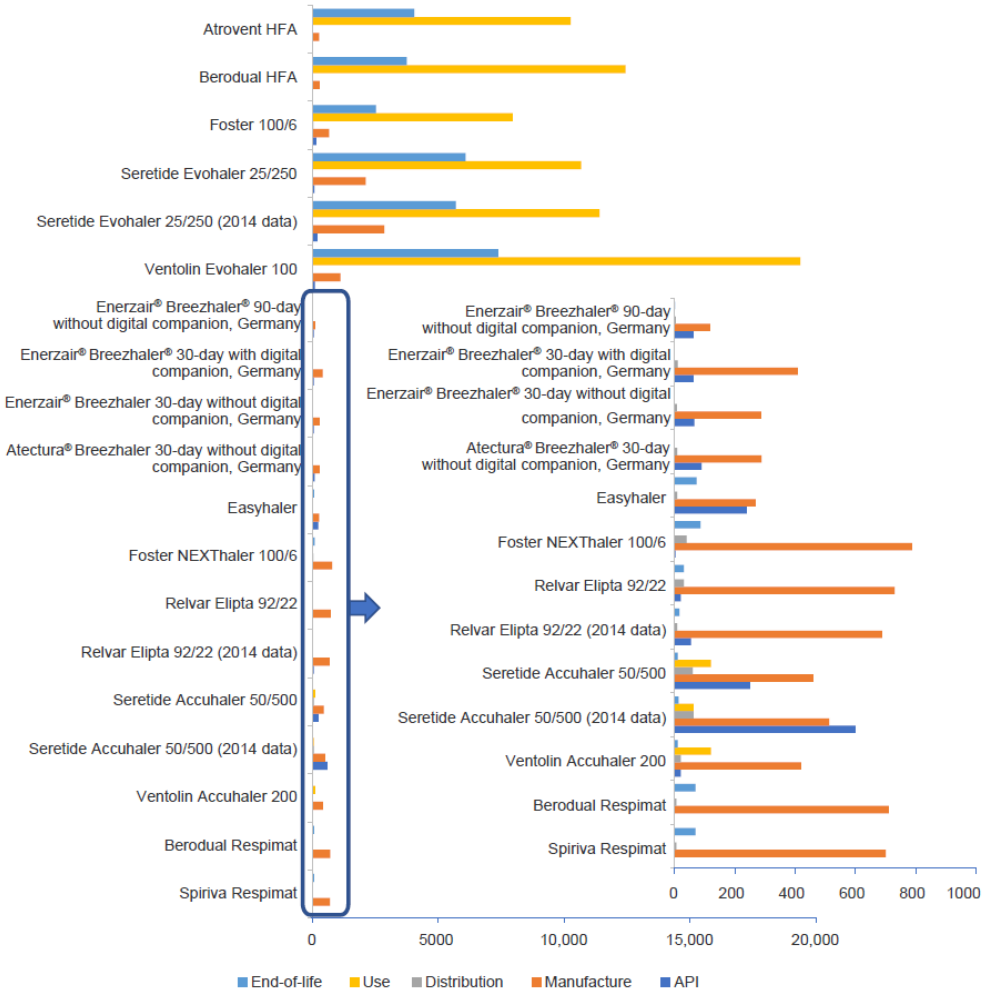

Figure 1. Breakdown of carbon footprint by life cycle stage. CFP, carbon footprint; HFA, hydrofluoroalkane.

Table 3. Breakdown of reported and calculated inhaler carbon footprint data by life cycle stage.

Device Name	Device Type	API		Manufacture		Distribution		Use		End-of-Life	
		gCO_2e	%	gCO_2e	%	gCO_2e	%	gCO_2e	%	gCO_2e	%
Atrovent HFA [9]	MDI	Incl. in mnfctr.	Incl. in mnfctr.	269	1.84	8	0.06	10260	70.35	4048	27.75
Berodual HFA [8]	MDI	Incl. in mnfctr.	Incl. in mnfctr.	287	1.74	3	0.02	12442	75.48	3752	22.76
Clenil Modulite 100 [8]	MDI	-	-	-	-	-	-	-	-	-	-
Clenil Modulite 200 [8]	MDI	-	-	-	-	-	-	-	-	-	-
Foster 100/6 [8]	MDI	154.10	1.36	659.40	5.82	39.70	0.35	7952.80	70.19	2524.40	22.28
Foster 200/6 [8]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Atrovent) [7]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Clenil) [7]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Flutiform) [7]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Foster) [7]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Salamol) [7]	MDI	-	-	-	-	-	-	-	-	-	-
Generic (i.e., Salmeterol) [7]	MDI				-	-	-	-	-	-	-
Generic (i.e., Ventolin) [7]	MDI				-	-	-	-	-	-	-
Seretide Evohaler 25/250 [6]	MDI	80	0.42	2120	11.16	30	0.16	10680	−56.21	6080	32.00
Seretide Evohaler 25/250 (2014 data) [11]	MDI	203.70	1.00	2852	14.00	0	0.00	11407	56.00	5703.60	28.00
Trimbow [8]	MDI	-	-	-	-	-	-	-	-	-	-
Ventolin Evohaler 100 [6]	MDI	100	0.36	1110	3.96	20	0.07	19390	69.25	7380	26.36
Breezhaler® 30-day without digital companion, used in Germany (without glycopyrronium bromide in API) [14]	DPI	88.32	23.00	288.00	75.00	7.68	2.00	0.0	0.00	0.00	0.00
Breezhaler® 30-day without digital companion, used in Germany [14]	DPI	64.62	18.00	287.20	80.00	7.18	2.00	0.0	0.00	0.00	0.00
Breezhaler® 30-day with digital companion, used in Germany [14]	DPI	62.53	13.00	408.85	85.00	9.62	2.00	0.0	0.00	0.00	0.00
Breezhaler® without digital companion (90-day) used in Germany [14]	DPI	62.56	34.00	117.76	64.00	3.68	2.00	0.0	0.00	0.00	0.00
Easyhaler [10]	DPI	238.93	40.60	268.36	45.6	8.24	1.40	0.00	0	72.39	12.30
Foster NEXThaler 100/6 [8]	DPI	2.20	0.24	788.60	86.13	39.30	4.29	0	0.00	85.50	9.34
Foster NEXThaler 200/6 [8]	DPI	-	-	-	-	-	-	-	-	-	-
Relvar Elipta 92/22 [6]	DPI	20	2.50	730	91.25	30	3.75	0	0.00	30	3.75
Relvar Elipta 92/22 (2014 data) [11]	DPI	53.50	7.00	688.20	90.00	7.60	1.00	0	0.00	15.3	2.00
Seretide Accuhaler 50/500 [6]	DPI	250	27.78	460	51.11	60	6.67	120	13.33	10	1.11
Seretide Accuhaler 50/500 (2014 data) [11]	DPI	600	48.00	512.50	41.00	62.50	5.00	62.5	5.00	12.5	1.00
Ventolin Accuhaler 200 [6]	DPI	20	3.33	420	70.00	20	3.33	120	20.00	10	1.67
Berodual Respimat [9]	SMI	Incl. in mnfctr.	Incl. in mnfctr.	710	90.61	5	0.65	0	0.00	69	8.90
Spiriva Respimat [9]	SMI	Incl. in mnfctr.	Incl. in mnfctr.	701	90.45	5	0.65	0	0.00	69	8.90

HFA, hydrofluoroalkane.

The use and end-of-life stages together contribute to most of the CFP of the MDI inhalers, typically in excess of 85%. In the case of the Berodual HFA device, the use and end-of-life stages contribute 98.24% of the total footprint. The size of the contribution to the use and end-of-life phases is a result of the release of HFA 134a and HFC 227a propellant, having high GWPs of 1300 and 3350, respectively [2]. Certain aspects of the disposition of propellant fate are not documented in the sources and have been determined based on assumptions made by the authors and device designers.

The largest contributions to the CFPs of the DPI/SMI inhalers are made by the API and during the manufacturing stages of the life cycle. The highest single contribution to the CFP of a DPI/SMI inhaler is made at the manufacturing stage, which, in the case of the Relvar Elipta 92/22 device, is 91.25%. The lowest contribution of manufacturing to a DPI/SMI device is 41%, in the case of the Seretide Accuhaler 50/500, quoted by the Carbon Trust in 2014 [11]. In this case, the contribution made by the API is 48.00%, representing 600 gCO_2e, the highest footprint of the API in an inhaler reported in any of the studies. For the Breezhaler® DPI (30-day IND/MF, IND/GLY/MF [30 days with and without a digital companion, 90 days without a digital companion]) from Germany, the largest contribution to the CFP is made by manufacturing.

When the API is not considered, since that is not driven by the inhaler type, contributions from the manufacturing life cycle stage to the overall CFP of a device are generally larger for MDI than for DPI/SMI, although the ranges overlap. The largest absolute contributions from the manufacturing stage are for an unspecified MDI at 2852 gCO_2e and 2120 for the Seretide Evohaler 25/250 MDI. Foster NEXThaler 100/6 has the highest contribution (788.60 gCO_2e) from the manufacturing life cycle to the CFP among DPIs/SMIs. Easyhaler®'s DPI has the lowest contribution from the manufacturing stage, at 268.36 gCO_2e. However, this is only slightly lower than the manufacturing contribution to the CFP by the Atrovent® HFA MDI, which is 269 gCO_2e (inclusive of API).

3.4. Life Cycle Impact Assessment of DPI and MDI

In order to assess legitimate concerns other than CFP and to avoid 'burden shifting' from one impact category to another, LCA assesses additional impact categories to provide a more comprehensive understanding of environmental effects and to avoid unintended consequences.

In an LCA of inhalers excluding API, following the ISO 14040/14044 guidelines, Jeswani and Azapagic considered 14 environmental impact categories that are included in the ReCiPe 2016 V1.1 impact assessment method [15]. These impacts were: global warming potential; fossil depletion; metal depletion; terrestrial acidification; freshwater eutrophication; marine eutrophication; carcinogenic human toxicity; non-carcinogenic human toxicity; freshwater ecotoxicity; marine ecotoxicity; terrestrial ecotoxicity; ozone depletion; photochemical oxidant formation for human health; and photochemical oxidant formation for ecosystems.

To examine whether other DPIs present similar impacts, and to examine the effect of the design on these, Fulford et al., conducted an LCA of the Breezhaler® device alone, excluding API [16]. Figure 2 presents the impact results for all inhalers studied by Jeswani and Azapagic and the results from the LCA study by Fulford et al., for Breezhaler® only in the German market, using a scale in which the impact of each device is presented as a percentage of that with the highest impact [15,16]. The generic DPI has the highest reported impacts for 6 of the environmental impact categories reported, whereas Breezhaler® has the highest impact for 4 impact categories. The HFA227ea MDI inhaler has the highest impact for 4 categories, and the HFA134a inhaler does not have the highest impact for any of the 14 impact categories and has the lowest impact in only 4 cases, the same as Breezhaler®. Overall, one or the other of the two DPIs has the highest impact for 10 of the 14 impact categories. However, where the generic DPI has the highest impact, Breezhaler® has the second highest impact for only 2 of the 6 impact categories. This clearly shows the relative impact of the two DPIs. In many

cases, the impact is not of a similar scale but is considerably different, often being more than 20% and being greater than 50% in 6 of the 14 impact categories. In these instances, the generic DPI has a lower impact than Breezhaler® against 2 impact categories, and Breezhaler® fares better than the generic DPI against the other 4 categories.

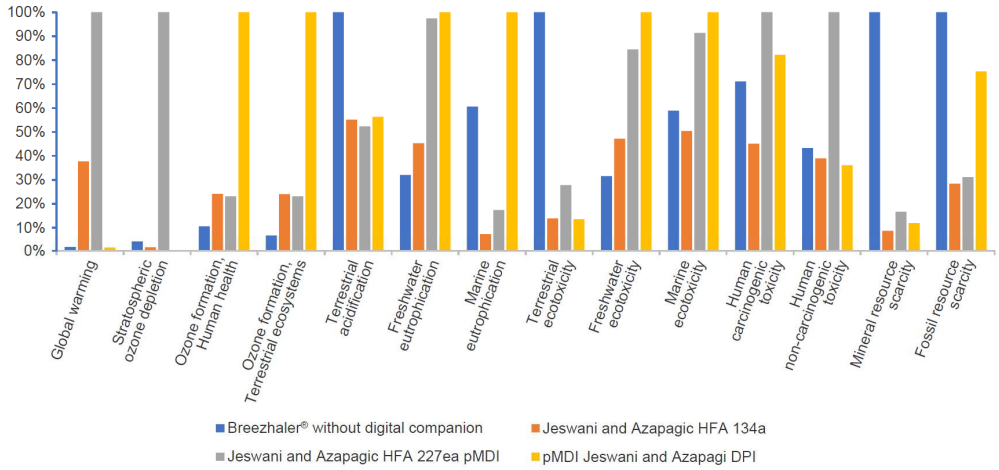

Figure 2. DPI and MDI Impact Assessment Results (ReCiPe 2016 V1.04). DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurized metered-dose inhaler. Note: LCA study system boundaries and assumptions may differ between the studies from which these results are drawn, to the extent that they should not be precisely compared.

Figure 3 presents the results of the Jeswani and Azapagic [15] and Fulford et al. [16] studies, normalized with respect to person equivalents, published by the National Institute for Public Health and the Environment Ministry of Health, Welfare and Sport in the Netherlands for the ReCiPe impact assessment method used in these LCAs. A person equivalent is a quantification of the environmental impact caused annually by the activities of an average citizen. Of the remaining impacts, the most significant with respect to person equivalents is global warming (or CFP). Furthermore, this is the only impact in which the difference in impact between devices exceeds an order of magnitude. With the exception of terrestrial ecotoxicology, for the other impacts, the contribution in person equivalents is lower, and the range between devices is much narrower.

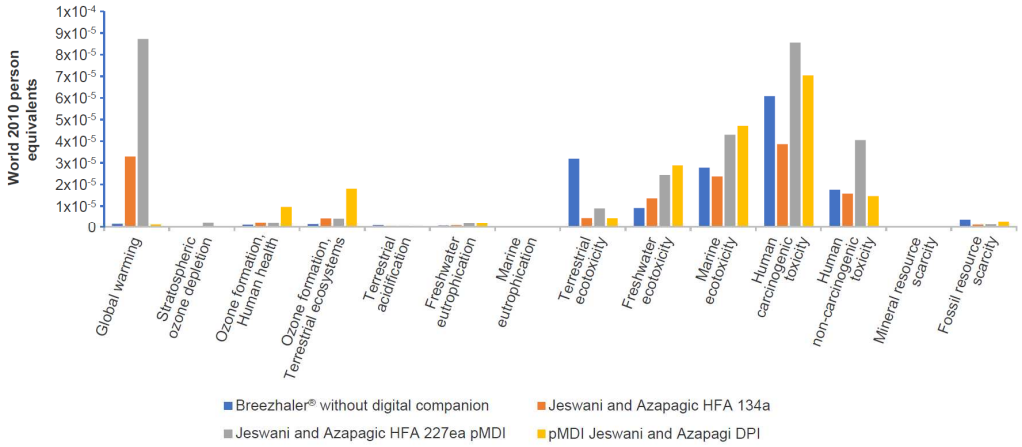

Figure 3. Impact assessment results normalized to person equivalents. DPI, dry powder inhaler; HFA, hydrofluoroalkane; pMDI, pressurized metered-dose inhaler. Note: LCA study system boundaries and assumptions may differ between the studies from which these results are drawn, to the extent that they should not be precisely compared.

4. Discussion

We reviewed data from recently published papers to understand the CFP of DPIs and MDIs. Generally, studies provide insufficient data regarding methodological differences and data quality, so we cannot comment with confidence on the extent to which choices and data affect CFP results. It can be expected that these matters have an influence on the precise CFP figures reported, and, as such, it is not possible to claim a like-for-like comparison, which limits the extent to which they can inform decision making. Some of the studies are independently verified as conformant with the relevant standard, e.g., the GHG Protocol. Many of the studies omit patient travel, although the GHG Protocol Product Standard Sector Guidance recommends that this is included. Additionally, the articles also contain many methodological discrepancies. For instance, in the study by Wilkinson et al., the focus of the analysis is on propellant use as a proxy for total CFP when the use of MDI and DPI/SMI is compared at the country level [7]. As a result, other life cycle stages, and perhaps all of them in the case of some data referenced in this study, were omitted in order to extend the reach of the analysis. This may have led to an underestimation of the CFP of some of the MDI devices included in the assessment.

Our review further validates the existing literature by establishing that the reported CFP of DPI devices is considerably lower than that of MDI inhalers and supports the preference to prescribe DPI devices by which clinical considerations are not affected. The CFP per inhaler of the inhalers evaluated ranged from 359 to 36,500 gCO_2e. Of all the devices compared, the highest CFP per actuation and per inhaler is for generic or unspecified MDI devices, whereas the lowest CFP for each functional unit per dose, per actuation and per inhaler is for Breezhaler® DPIs. The breakdown of inhaler CFP by life cycle stage reveals that, although the use and end-of-life stages together contribute most of the CFPs of the MDI inhalers, typically in excess of 85%, the largest contributions to the CFPs of the DPI/SMI inhalers are made by the API and manufacturing stages of the life cycle. The potential future use of HFA152a, a low-GWP propellant, is highlighted by the studies conducted by Jeswani and Azapagic [15] and by Panigone et al. [8]. A review of the life cycle impact assessment data on DPI and MDI using the Jeswani and Azapagic [15] and Fulford et al. [16] paper demonstrates that the generic DPI has the highest reported impacts for six of the environmental impact categories reported, whereas Breezhaler® has the highest impact for four impact categories.

However, although the generic DPI has the highest impact, Breezhaler® has the second highest impact for only two of the six impact categories. Although Breezhaler® has the highest impact, the generic DPI is second for only two of the four impact categories. This reveals a more complex picture than was originally evident from the Jeswani and Azapagic study [15]; a DPI may have higher impacts for some environmental impact categories other than CFP, as they reported, but this is not consistent across all DPI devices. As observed above in relation to the breadth of the DPI CFP, this is an artifact of the design and the materials used in the DPI and is not an inherent feature of the technology. As a result, it is possible to design or subsequently to select DPI devices with environmental impacts other than CFP in mind, if these are to be of concern.

Our review also demonstrates that it may be possible, disproportionately, to reduce the footprint of DPI/SMI by increasing the number of actuations and doses they deliver. Increasing the number of actuations per inhaler may further increase the benefit that can be derived from switching from MDI to DPI/SMI devices. The effect of this can be seen most clearly in the footprint of the Breezhaler®, where the device sold in a 90-day pack has a footprint that is much lower than that sold in a 30-day pack (≈51% lower, 6.33 gCO_2e per dose compared with 12.5 gCO_2e per dose). The CFP of the reusable Respimat device also falls significantly as refill cartridges extend its life from 30 days to 60 and 90 days (reductions of 51% and 71%, respectively). Therefore, increased lifetime and/or functionality should be an objective in the design and deployment of inhalers in the future.

It is also important to understand the environmental benefits of increased adherence achieved by smart inhalers. For example, although the GHG emissions associated with the digital companion accompanying the Breezhaler® are included, the study boundary excludes the potential benefits resulting from improved adherence and any positive impacts associated with reductions in asthma exacerbations and rescue medication use [16]. If the digital companion reduces exacerbations and the use of rescue medications, then the GHG emissions associated with these occurrences are similarly reduced, with the effect of counterbalancing the additional impacts of the digital companion. This balance was investigated in a study on the Smartinhaler™ Turbu+ EMD device, which concluded that around a 50% reduction in CFP can be achieved for a patient with poorly controlled asthma through improved adherence when using a DPI Smartinhaler device [17]. Investigations of the benefits of inhalers through the care pathway approach can help decision makers to optimize their carbon reduction potential and contribution in the future.

Based on the challenges faced while performing this review, we emphasize the need to standardize the study boundaries to facilitate more consistent comparison of CFPs and other life cycle impacts of different inhalers. It is also a good practice for studies to clearly state the method adopted, the compliance standards adhered to, the life cycle stages that were included and excluded and whether an independent review was conducted. Such standardized methods may pave the way to a future where the CFP of each product can be included in the label, making it easy for the medical community to comprehend and to compare the CFPs of different inhalers. Greater collaboration between academics and the industry can help to achieve this.

5. Conclusions

Our review establishes that the reported CFP of DPI devices is considerably lower than that of MDI inhalers. Despite the methodological challenges in comparing the CFPs of DPIs, our analysis reveals that the CFP does vary between different DPIs, ranging from 359 gCO_2e per inhaler (Enerzair Breezhaler® DPI without a digital companion, 30-day pack) to 1250 gCO_2e per inhaler (Seretide Accuhaler® 50/500) and from 6.13 gCO_2e per dose (Enerzair Breezhaler® DPI without a digital companion, 90-day pack) to 27 gCO_2e per dose (Relvar Elipta 92/22). The breakdown of inhaler CFP by life cycle stage reveals that, although the use and end-of-life stages together contribute most of the CFP of the MDI inhalers, the largest contributions to the CFP of the DPI/SMI inhalers are made by the API and manufacturing stages of the life cycle. From a climate perspective, our review aligns with the findings of Jeswani and Azapagic that DPIs have a lower CFP than pMDIs. Our analysis reveals that the performance against other environment impact categories depends on the design, choice of material and manufacturing process of the DPIs. Regardless, the clinical efficacy and safety of each medication should remain the factors informing clinical decisions. From a sustainability perspective, and to reduce the environmental impact of inhalers, our analysis suggests that this can be achieved in the short term by switching from pMDIs to DPIs and in the long-term by improving in the design of existing DPIs (e.g., by increasing the lifetime and/or functionality) combined with the assessment of the care pathways in which they are deployed. Our review is limited by apparent or reported variability in the methods or standards adopted by the included studies. The challenge of comparing the CFPs of different inhalers and other medical devices, pharmaceuticals and care pathways can be made easier by the standardization of study boundaries and methods in the future.

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Conflicts of Interest: Brett Fulford and Karen Mezzi are employees of Novartis, Pharma AG, Basel, Switzerland. Simon Aumônier is a Partner at ERM. ERM is a global sustainability consulting business that works widely on a broad range of assignments for clients across all sectors of the economy. Its work has included pro bono contributions and consulting assignments for the Sustainable Healthcare Coalition and consulting engagements with many pharmaceutical and medical device companies, including Novartis Pharma AG. Matthias Finkbeiner is the Chair of Sustainable Engineering and Managing Director of the Department of Environmental Technology at the Technical University of Berlin.

Abbreviations

API	active pharmaceutical ingredient
CFP	carbon footprint
GWP	global warming potential
HFA	hydrofluoroalkane
HFC	hydrofluorocarbon
ICS	inhaled corticosteroid
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
LCA	life cycle assessment
NHS	National Health Service
pMDI	pressurized metered-dose inhalers
SMI	soft mist inhalers

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