Impact of Asthma Inhalers on Global Climate: A Systematic Review of Their Carbon Footprint and Clinical Outcomes in Spain

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J Investig Allergol Clin Immunol 2023; Vol. 33(4): 250-262
doi: 10.18176/jiaci.0887

Abstract

Background: Pressurized metered-dose inhalers (pMDIs) exert an environmental impact resulting from CO_2 emissions. Therapeutic alternatives with less environmental impact are widely used. Nevertheless, the choice of device and appropriate therapy should meet the clinical needs and the characteristics of the patient.
Objective: The primary objective was to estimate the impact of pMDIs prescribed for any indication on annual CO_2 emissions in Spain. The secondary objective was to evaluate the potential impact of switching pMDIs to dry-powder inhalers (DPIs) in patients with asthma.
Methods: A systematic review of the evidence published during 2010-2021 was carried out. Average annual CO_2 emissions of DPIs and pMDIs were calculated in 2 scenarios: the current situation and a hypothetical situation involving a switch from all pMDIs to DPIs. The impact of the switch on clinical outcomes was also evaluated.
Results: The total value of CO_2-eq/year due to DPIs and pMDIs accounted for 0.0056% and 0.0909%, respectively, of total emissions in Spain. In the event of switching pMDIs to DPIs, except those used for rescue medication, the percentages were 0.0076% and 0.0579%. The evaluation of efficacy, handling, satisfaction, safety, and use of health care resources was not conclusive.
Conclusions: Current CO_2 emissions by pMDIs account for a small percentage of the total CO_2 footprint in Spain. Nevertheless, there is a need for research into new and more sustainable devices. Suitability and patient clinical criteria such as age and inspiratory flow should be prioritized when prescribing an inhaler.

Key words: Asthma. Inhaler devices. Metered-dose inhalers. Antiasthmatic agents. Carbon footprint. Climate change. Global warming. Environment.

Resumen

Antecedentes: Los inhaladores presurizados de dosis medidas (pMDI) tienen cierto impacto sobre las emisiones de CO_2. Existen alternativas terapéuticas con menor impacto que están siendo ampliamente utilizadas. Sin embargo, la elección del dispositivo y del tratamiento debe considerar las necesidades clínicas y características del paciente.
Objetivo: El objetivo principal fue estimar el impacto de los pMDI, prescritos para cualquier indicación, en las emisiones anuales de CO_2 en España. En segundo lugar, evaluamos el impacto potencial del cambio de pMDI a inhaladores de polvo seco (DPI) en pacientes con asma.
Métodos: Se realizó una revisión sistemática de la evidencia publicada entre 2010-2021. Se calculó la media de emisiones anuales de CO_2 de DPI y pMDI en dos escenarios: situación actual y una hipotética de cambio de los pMDI por DPI. Se evaluó el posible impacto clínico del cambio.
Resultados: El valor total de CO_2-eq/año derivado del uso de DPI y pMDI supone, respectivamente, el 0,0056% y el 0,0909% de las emisiones totales en España. Estos porcentajes serían 0,0076% y 0,0579% substituyendo los pMDI por DPI, excepto la medicación de rescate. La evaluación de la eficacia, manejo, satisfacción, seguridad y utilización de recursos no fue concluyente.
Conclusión: Las emisiones actuales de CO_2 derivadas de los pMDI representan un pequeño porcentaje de la huella total de CO_2 en España. Es necesario desarrollar nuevos dispositivos más sostenibles y con menor huella de carbono. La idoneidad de los inhaladores y los criterios clínicos de los pacientes (edad o flujo inspiratorio) deben priorizarse en la prescripción.

Palabras clave: Asma. Dispositivos inhaladores. Inhaladores de dosis medidas. Agentes antiasmáticos. Huella de carbono. Cambio climático. Calentamiento global. Medio ambiente.

Introduction

Asthma is a very common chronic inflammatory respiratory disease that presents with symptoms such as wheezing, shortness of breath, feeling of chest tightness, and cough [1]. According to the World Health Organization, 262 million people had asthma in 2019 [2]. In Spain, 5%-14% of the population is affected by asthma [3], and 1134 deaths were attributable to this disease in 2015 [4]. Most drugs used for asthma treatment are inhaled [1]. The several types of commercially available inhalers include pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), liquid multidose spray devices (eg, soft mist inhalers [SMIs]), nebulizers, and spacer chambers. Patterns of prescription of inhalers for any disease differ across Europe [5], although pMDIs, which are used worldwide, are the most frequently prescribed [6]. In Spain, some 30 million inhalers were consumed in 2020; of these, 48% were pMDIs, 45% DPIs, and 7% SMIs [7,8]. Each type of inhaler has advantages and disadvantages in terms of portability, ease and speed of use, and cost [9-11]. While a correlation between patient satisfaction with adherence and disease control has only been shown in observational studies [12,13], it is important to guarantee patient satisfaction with the selected devices. Moreover, adherence is frequently poor in asthma patients [14], with the consequent negative impact on disease control [15,16].

Beyond the improvement in clinical outcomes obtained with the different types of inhalers, the potential impact of these devices on CO_2 emissions and the environment is currently being debated. Historically, pMDIs contained chlorofluorocarbon (CFC) propellants. CFCs were banned following the Montreal Protocol of 1987, which took effect in 1989, owing to their ozone-depleting effect [17]. Subsequently, CFC propellants were replaced by hydrofluorocarbons (HFCs) in the formulation of pMDIs. Although HFCs do not have an ozone-depleting effect, they are classified as greenhouse gases with global warming potential. According to the Kyoto Protocol, adopted in 1997, the use of HFCs and other greenhouse gases must be progressively phased out [18]. In 2016, the Kigali Amendment to the Montreal Protocol was signed to gradually reduce the consumption and production of HFCs [19]. Similarly, EU Regulation 517/2014 provides for the reduction of fluorinated gases owing to their greenhouse effect. Nevertheless, in 2014, this regulation exempted pharmaceutical products from the phase-down. The recent proposal of the regulation under revision removed the exemption and commands progressive reduction in inhaler-derived CO_2 emissions in order to guarantee patient access to proper treatment of respiratory disease. Along these lines, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Family and Community Medicine (semFYC) [20] have considered the possibility of prioritizing DPIs and SMIs over pMDIs, although only when patient characteristics are appropriate [21,22]. However, they have also underlined that switching inhalation devices for environmental reasons could have health and economic consequences [23]. Additionally, the current Spanish guideline GEMA 5.2 states that switching inhalers for nonclinical reasons could worsen adherence and symptoms [24]. The GOLD 2023 international guidelines on management of chronic obstructive pulmonary disease (COPD) also call for joint decision making between the prescriber and the patient, taking into account the attributes of the inhaler device and the patient's abilities [25].

Based on randomized clinical trials mostly performed with DPIs, the Global Initiative for Asthma (GINA) supports the use of as-needed inhaled corticosteroids (ICS)/formoterol as rescue medication and highlights the risk of the excessive use of short-acting ß-2 agonists (SABAs) with respect to exacerbations [1]. However, real-world practice differs markedly from the GINA recommendation, and approximately one-third of asthma patients in Spain are prescribed 3 or more SABA canisters per year [26], with the resulting economic and environmental consequences [27,28].

In May 2021, the European Respiratory Society published a position statement on asthma and environment, defending that efficacy, safety, and patient choice must continue to be the primary drivers in deciding the most suitable inhaler for asthma patients [29]. Patient organizations have also taken a stand on the matter [30,31].

As reported in several studies, the environmental impact of inhalers differs for each specific product. We hypothesized that, in Spain, the avoidance of pMDIs as a strategy to eliminate their low contribution to CO_2 emissions could have a major impact on patient clinical outcomes. Consequently, we intended to estimate the impact of pMDIs on CO_2 emissions in Spain and to evaluate the potential impact of switching prescriptions of pMDIs to DPIs in patients with asthma following exclusively environmental criteria. Nebulizers were not included as they are infrequently used; likewise, spacer chambers are accessory devices to facilitate the inhalation technique but do not exert an impact on CO_2 emissions.

Methods

Design

A systematic review of the evidence was conducted by 2 independent experts in the methodology used for this research (Gloria González and Sara García). The entire process was supervised and reviewed by the remaining authors of this publication. Two research questions were formulated, the second one following the Patient, Intervention, Comparison, Outcome (PICO) method [32]:

- RESEARCH QUESTION 1: What is the impact of pMDIs on CO_2 emissions?
- RESEARCH QUESTION 2: What is the potential impact of switching asthma treatment from pMDIs to DPIs (whenever possible) on efficacy, quality of life, handling, adherence, satisfaction, safety, and health care resources?

Search Strategy

Several preliminary search strategies, including different key words and MeSH terms, were designed and implemented for both questions. The most suitable strategy was chosen according to the results obtained (Supplementary material 1). The search was carried out in both the PubMed database and the Cochrane Library without filters and within predefined time limits from 2010 to 2021, as throughout this time frame the importance of the carbon footprint had begun to be

emphasized. A total of 24 randomized clinical trials published prior to 2010 were also reviewed. Half of these trials analyzed the equivalence/noninferiority of pMDI and DPI devices and supported the idea that devices do not influence the efficacy of the molecules used for asthma treatment [33-38]. The other half studied the efficacy and safety profile of various types of pMDI, patient perception, adherence, and inhalation profiles in asthma and COPD. No software was used for the search, and publications were extracted directly from databases to an XML file and to Mendeley Reference Manager. An ascending search was carried out, and the bibliographic references of the publications selected were reviewed; those published within the predefined time limits were also included in the analysis. Following the removal of duplicates, all the publications were screened by title and abstract, and the selection criteria were checked by 2 reviewers.

Selection of Publications and Data Collection

Publications in languages other than English or Spanish were identified but are excluded from the PRISMA flowchart (Figure 1). Publications without an abstract and unpublished studies were also excluded. The full texts of all the studies fulfilling the selection criteria (Supplementary material 2) were retrieved. Both reviewers extracted the data that provided information to answer the research questions on a standardized form that included study characteristics, evaluation variables, and results. A preliminary extraction of information from 2 studies was carried out by the 2 reviewers, and the information was compared to check consistency. A third reviewer checked a random sample of 15% of the records and resolved any disagreements between the main reviewers. The publications that were excluded and the reasons why are provided in Supplementary material 3. All the outcome units provided in each publication were extracted.

Assessment of Study Quality

Confounding was not assessed, although characteristics that were potentially confounding variables were recorded in the database. The evaluation of the quality of the studies and the factors that could potentially introduce bias or limit the extrapolation of results for both questions was carried out by 2 independent reviewers using the Mixed Methods Appraisal Tool (MMAT) [39]. Publications with a MMAT score >60 were considered high-quality and were included in the critical appraisal (Supplementary material 4 and 5). A sensitivity analysis was performed comparing the data obtained from all the publications regardless of their MMAT score, with the data extracted from publications with a MMAT score >60.

Analysis

Data regarding the carbon footprint of DPIs and pMDIs were heterogeneous; therefore, the units were homogenized. For 2 publications showing carbon footprint per dose, the data were recalculated to carbon footprint per pack [40,41]. The number of doses per pack was obtained from the Online Centre of Information of Authorized Medicines of the Spanish Agency of Medicines and Medical Devices [42]. The data

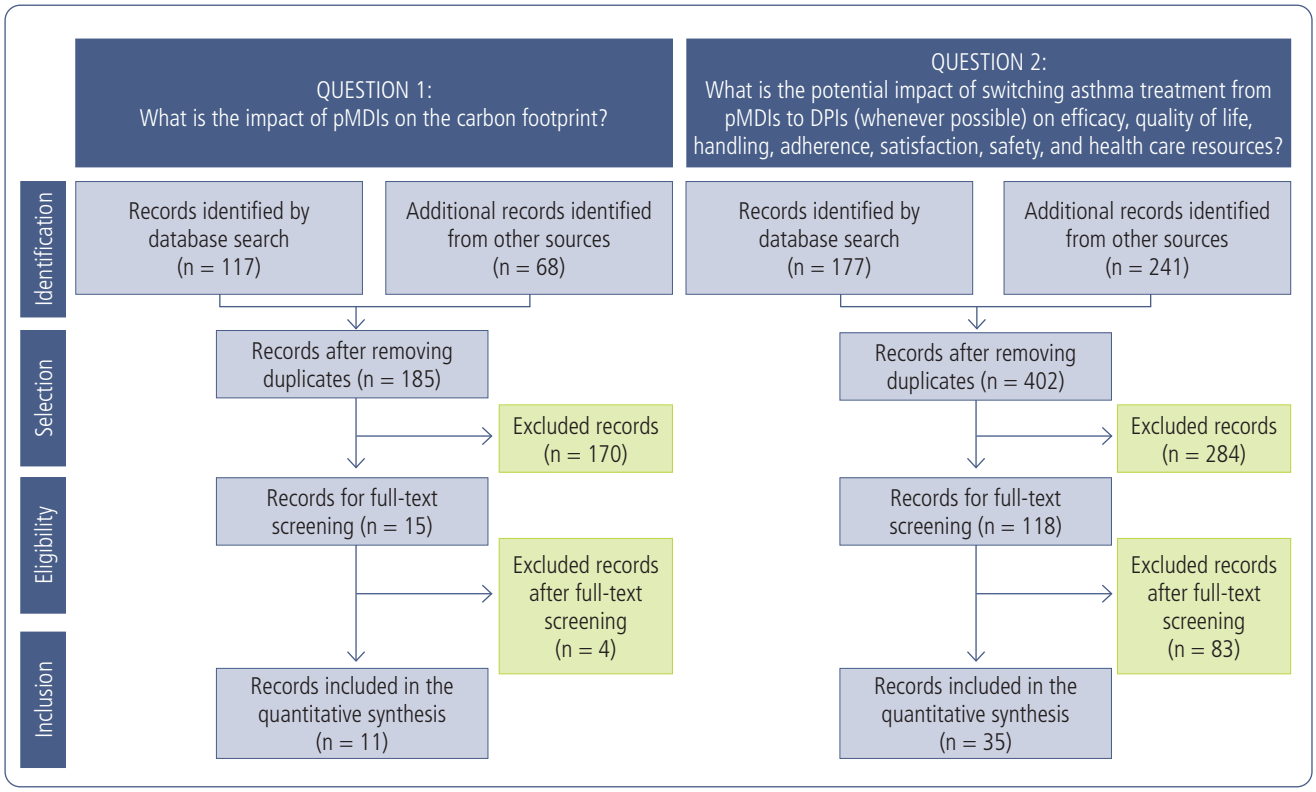

Figure 1. PRISMA flowchart. pMDIs indicates pressurized metered-dose inhalers; DPIs, dry-powder inhalers.

extracted in the original units of measure of each study were reconverted into kg of CO_2-equivalent using the automatic calculator provided by the Environmental Protection Agency (EPA) [43]. The mean annual carbon footprint of DPIs and pMDIs was calculated and multiplied by the number of packs of inhalers sold in 2020 for asthma or any other indication (probably overestimating the asthma carbon footprint in Spain), as reported by IQVIA [8]. The total value of DPI- and pMDI-associated CO_2 emissions (absolute values and percentage of total emissions) was calculated in 2 scenarios: (*1*) the present situation, considering current data on DPI and pMDI units sold in 2020; and (*2*) a hypothetical situation: considering a potential switch of all pMDIs sold in 2020 to DPIs, with the exception of those containing SABAs, which account for the most prescribed pMDIs in Spain and are the largest contributors to global emissions of all pMDI devices. This exception was made, since pMDIs containing SABAs are commonly used as rescue medication by asthma patients and, therefore, are more difficult to replace.

Given the considerable heterogeneity of outcomes found for QUESTION 2, statistically significant results ($P<.05$) were counted as significant for either of the options (DPIs or pMDIs) and those without statistical significance ($P>.05$) as nonsignificant. In publications with no direct comparison, when the *P* value was not provided, or when the data were descriptive, the results were counted as undetermined. The numbers of statistically significant outcome units favoring DPIs or pMDIs were summed.

Results

Overview of the Studies Included

A total of 185 publications were found for QUESTION 1 following the exclusion of duplicates. Of these, 170 were excluded following title/abstract screening and 4 after full-text screening. A total of 11 publications were considered, and 8 were included in the analysis. The other 3 were disregarded as they did not provide per pack, dose, or actuation data. A total of 403 publications were collected for QUESTION 2 following the exclusion of duplicates. Of these, 284 were excluded following title/abstract screening and 83 after full-text screening. A total of 35 publications were included in the analysis (Figure 1).

Supplementary material 4 summarizes the characteristics and the results of each publication on asthma treatment reporting the inhaler-derived carbon footprint. Supplementary material 5 summarizes the characteristics of publications reporting the clinical outcomes of patients with asthma treated with either pMDIs or DPIs.

Carbon Footprint

The inhalers' carbon footprint values were extracted from all the publications selected for QUESTION 1 and converted to kg CO_2-eq/year/pack (Supplementary material 4). The mean value of kg CO_2-eq/year/pack was 16.69 for pMDIs, 1.02 for DPIs, and 0.59 for SMIs. Considering annual sales of each type of inhaler throughout 2020, the carbon footprint was 230 108.34 t CO_2-eq/year for pMDIs, 14 273.87 t CO_2-eq/year for DPIs, and 1241.79 t CO_2-eq/year for SMIs. Given that the average annual greenhouse gas emission in Spain during the 2016-2020 period was 2.53×10^8 t, pMDIs, DPIs, and SMIs accounted for 0.0909%, 0.0056%, and 0.0005% of the annual emissions, respectively.

A hypothetical scenario of a switch from all prescribed pMDIs to DPIs in Spain, with the exception of those containing SABAs, was simulated. A total of 5 001 484 packs of pMDIs could be switched to DPIs and 8 783 159 packs would continue to be pMDIs because they correspond to SABA units. This situation would constitute a carbon footprint of 146 618.10 t CO_2-eq/year due to pMDIs and of 19 368.45 t CO_2-eq/year due to DPIs, accounting for 0.0579% and 0.0076% of total emissions, respectively (Table 1).

Impact of the Inhaler on Clinical Outcomes

Efficacy

A total of 26 publications addressed the efficacy of pMDIs and/or DPIs. Of these, 21 addressed asthma control (asthma control, exacerbations, hospitalization rate, asthma severity, oxygen saturation, SABA use, inhaled corticosteroid use, oral corticosteroid use, leukotriene receptor antagonist use, systemic antibiotic use, asthma control days, symptom-free days, SABA-free days, awakening-free nights, Asthma Control Test score, Asthma Control Questionnaire score, daytime symptoms score, night-time symptoms score, wheezing score, accessory muscle score, asthma control score, caregiver assessment, physician assessment, risk domain for asthma

Table 1. Calculations of Carbon Footprint Due to DPIs and pMDIs in the Current Situation and in a Hypothetical Situation of Switch From pMDIs to DPIs.

	Current situation		Hypothetical situation[a]	
	DPIs	pMDIs	DPIs	pMDIs
Mean carbon footprint/pack, kg CO_2-eq/year/pack	1.02	16.69	1.02	16.69
Packs sold in 2020 in Spain [8]	14 013 040	13 784 643	19 014 584	8 783 159
Total value of carbon footprint, t CO_2-eq/year	14 273.87	230 108.34	19 368.45	146 618.10
Percentage of carbon footprint due to inhalers vs global[b]	0.0056%	0.0909%	0.0076%	0.0579%

Abbreviations: DPIs, dry-powder inhalers; pMDIs, pressurized metered-dose inhalers
[a]Conversion of all pMDIs sold in Spain in 2020 to DPIs, except packs that correspond to SABA.
[b]Global greenhouse gas emissions were calculated using the annual values from 2016 to 2020 in Spain (https://ourworldindata.org/co2-emissions). The mean value was 2.53×10^{11} kg.

control, Borg dyspnea score, treatment success, limitation in physical activity, clinical improvements, asthma-worsening events or withdrawal due to worsening), 18 addressed lung function (fractional exhaled nitric oxide, spirometry, forced oscillation technique, body plethysmography, and lung function), 1 addressed duration of response, and 1 addressed time to response.

A pool of 21 publications presented an MMAT score >60. Of a total of 189 efficacy units found in these publications, 112 did not show significant differences, 52 favored pMDIs, and 5 favored DPIs. No significant differences were recorded for 31 asthma control units, 30 favored pMDIs, and 1 favored DPIs. No significant differences were observed for 80 lung function units, 22 favored pMDIs, and 4 favored DPIs. No duration of response or time to response unit favored either DPIs or pMDIs (Table 2, Figure 2).

In the sensitivity analysis, which included all publications regardless of their MMAT score, no significant differences were recorded for 130 efficacy units, 56 favored pMDIs, and 5 favored DPIs (Supplementary material 6). Results according to the drugs used in each publication are also shown in Supplementary material 13.

Quality of Life

Two publications addressed the quality of life of patients treated with pMDIs and/or DPIs and provided data on the following outcomes: limitation of activities of daily living, the Pediatric Asthma Quality of Life Questionnaire (PAQLQ) score, and the Asthma Health Questionnaire (AHQ)-33-Japan score.

Only 1 publication presented an MMAT score >60 [44], and the 2 quality of life units found favored pMDIs.

After the sensitivity analysis, which included all the publications regardless of their MMAT score, 2 quality of life units favored pMDIs, no significant differences were recorded

Table 2. Efficacy Outcomes According to the Type of Inhaler in Publications With an MMAT Score >60.

Endpoint (publication)	Favoring DPIs	Favoring pMDIs	Undetermined	Not significant	Total
Asthma control [44] [45] [46] [47] [61] [62] [63] [64] [65] [66] [67][68] [69] [70] [71] [72] [73]	1	30	17	31	79
Duration of response [77]			1	1	2
Lung function [44] [45] [61] [62] [63] [66] [67] [68] [69] [70] [74] [75] [76] [77]	4	22	1	80	107
Time to response [77]			1		1
Total	5	52	20	112	189

Abbreviations: DPIs, dry-powder inhalers; MMAT, Mixed Methods Appraisal Tool; pMDIs, pressurized metered-dose inhalers.

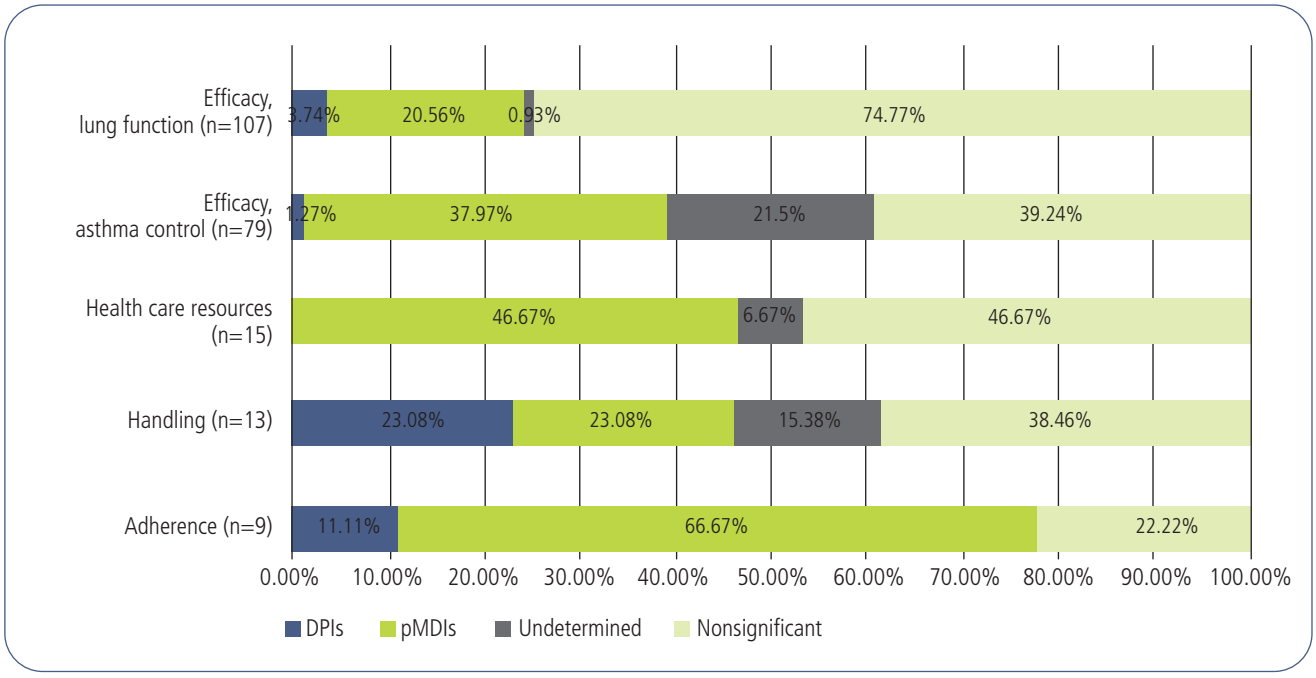

Figure 2. Percentage of outcomes favoring each type of inhaler, with undetermined or with nonsignificant results in publications with the Mixed Methods Appraisal Tool >60. pMDIs indicates pressurized metered-dose inhalers; DPIs, dry-powder inhalers.

for 1, and none favored DPIs (Supplementary material 7). The results according to the drugs used in each publication are also shown in Supplementary material 14.

Handling

A total of 11 publications addressed the handling of pMDIs and/or DPIs and provided data on the following outcomes: correct technique, technique score, error rate, time to correct use, critical errors, ease of use, overall errors, and patients requiring instructions.

Seven publications presented an MMAT score >60, and of 13 handling units found in them, no significant differences were recorded for 5, 3 favored DPIs, and 3 favored pMDIs (Table 3, Figure 2).

After the sensitivity analysis, including all the publications regardless of their MMAT score, no significant differences were recorded for 11 handling units, 5 favored DPIs, and 5 favored pMDIs (Supplementary material 8). Results according to the drugs used in each publication are also shown in Supplementary material 15.

Adherence

Seven publications addressed adherence in patients treated with pMDIs and/or DPIs and provided data on the following outcomes: Medication Adherence Questionnaire score, adherence, changes in therapy, <50% adherence, persistence, duration of treatment, and treatment possession.

Six publications presented an MMAT score >60. Nine adherence units were found; of these, 6 favored pMDIs, 2 did not report significant differences, and 1 favored DPIs (Table 4, Figure 2).

After the sensitivity analysis, including all the publications regardless of their MMAT score, 6 adherence units favored pMDIs, 3 did not report significant differences, and 1 favored DPIs (Supplementary material 9). Results according to the drugs used in each publication are also shown in Supplementary material 16.

Satisfaction

Six publications addressed the satisfaction of patients treated with pMDIs and/or DPIs and provided data on the following outcomes: Treatment Satisfaction Questionnaire for Medication score, asthma knowledge questionnaire for consumers score, patient satisfaction questionnaire, Asthma Treatment Satisfaction Measure score, and preference.

Three publications presented an MMAT score >60 [45-47]. Five satisfaction units were found. No significant differences were reported for 3 of these, 2 favored pMDIs, and none favored DPIs.

In the sensitivity analysis, which included all the publications regardless of their MMAT score, no significant differences were reported for 5 satisfaction units, 3 favored pMDIs, and none favored DPIs (Supplementary material 10).

Table 3. Handling Outcomes According to the Type of Inhaler in Publications With an MMAT Score >60.

Endpoint (publication)	Favoring DPIs	Favoring pMDIs	Undetermined	Not significant	Total
Correct technique [46] [70] [78]		2	1	1	4
Critical errors [79]				1	1
Ease of use [79]	1				1
Error rate [80] [81]	1		1		2
Overall errors [79]				1	1
Patient requiring instructions [79]				1	1
Technique score [46]		1			1
Time to correct use [79] [82]	1			1	2
Total	3	3	2	5	13

Abbreviations: DPIs, dry-powder inhalers; MMAT, Mixed Methods Appraisal Tool; pMDIs, pressurized metered-dose inhalers.

Table 4. Adherence Outcomes According to the Type of Inhaler in Publications With an MMAT Score >60.

Publication	Favoring DPIs	Favoring pMDIs	Undetermined	Not significant	Total
Adherence score [45]		1			1
Change in therapy [65]		1			1
Treatment persistence [65] [66] [70] [72] [83]	1	4		2	7
Total	1	6		2	9

Abbreviations: DPIs, dry-powder inhalers; MMAT, Mixed Methods Appraisal Tool; pMDIs, pressurized metered-dose inhalers.

Table 5. Safety Outcomes According to the Type of Inhaler in Publications With an MMAT Score >60.

Endpoint (publication)	Favoring DPIs	Favoring pMDIs	Undetermined	Not significant	Total
Bronchitis [70]				1	1
Cold [63]				1	1
Dyspnea [63]				1	1
Electrocardiogram deviations [63]				1	1
Headache [63] [70]				2	2
Heart rate [44] [63]			1	1	2
Hoarseness [63]				1	1
Laboratory test abnormalities [63]				1	1
Mild adverse events out of all adverse events [63]				1	1
Nasopharyngitis [70]				1	1
Oral thrush [44] [70] [73]			1	2	3
Overall adverse events [44] [68] [76] [84]			8	1	9
QT interval [44]			1		1
Rhinitis [70]			1		1
Serum glucose [44]			1		1
Serum potassium [44]			1		1
Throat discomfort [70]				1	1
Throat irritation [70]				1	1
Voice change [70]				1	1
Total	0	0	14	17	31

Abbreviations: DPIs, dry-powder inhalers; MMAT, Mixed Methods Appraisal Tool; pMDIs, pressurized metered-dose inhalers.

Results according to the drugs used in each publication are also shown in Supplementary material 17.

Safety

A total of 12 publications addressed the safety of DPIs or pMDIs. Some assessed the overall rate of adverse events and others reported the occurrence of specific adverse events.

A total of 31 safety units were found in 7 publications with MMAT >60. No significant differences were found for 17 of these, and none favored either DPIs or pMDIs (Table 5).

After the sensitivity analysis, including all the publications regardless of their MMAT score, 29 safety units did not show significant differences, 1 favored pMDIs, and none favored DPIs (Supplementary material 12). Results according to the molecules used in each publication are also shown in Supplementary material 18.

Use of Health Care Resources

Three publications addressed the use of health care resources in patients treated with pMDIs and/or DPIs and provided data on the following outcomes: caregiver off work, caregiver routine interrupted, visits to the emergency room, phone calls to the doctor, unscheduled visits to the doctor, complementary tests, days off work, in-hospital visit, hospital admissions, hospitalization days, laboratory tests, visits to the family doctor, and x-rays.

All 3 publications presented an MMAT score >60. Fifteen units regarding the use of health care resources were found. No significant differences were recorded for 7 of them, 7 favored pMDIs, and none favored DPIs (Table 6, Figure 2). The results according to the drugs used in each publication are also shown in Supplementary material 19.

Discussion

This work includes a review of the scientific evidence on CO_2 emissions from pMDIs, SMIs, and DPIs used to treat asthma and an analysis of the impact of a hypothetical switch from pMDIs to DPIs on clinical outcomes. pDMIs have been estimated to account for 0.0909% of total CO_2 emissions per year in Spain. In the United Kingdom, where pMDIs are used more frequently than in Spain (both in proportion to DPI and in absolute values) [48], emissions due to pMDIs account for 0.1% of the total national carbon footprint and 3.1% of the National Health Service carbon footprint [49,50]. In the United States, the discharge and leakage of hydrofluoroalkanes (HFAs) from pMDIs has been reported to generate 2500 kt CO_2-eq [51]. Worldwide emissions due to pMDIs have been reported to

Table 6. Outcomes for Use of Health Care Resources According to the Type of Inhaler in Publications with an MMAT Score >60.

Endpoint (publication)	Favoring DPIs	Favoring pMDIs	Undetermined	Not significant	Total
Caregiver off work [44]				1	1
Caregiver routine interrupted [44]				1	1
Complementary tests [66]		1			1
Days off work [66]				1	1
Doctor in-hospital visit [66]				1	1
Hospital admissions [66]				1	1
Hospitalization days [66]		1			1
Laboratory tests [66]		1			1
Phone calls to doctor [44]				1	1
Unscheduled visit to doctor [44]				1	1
Visits to emergency department [44] [66] [70]		2	1		3
Visits to family doctor [66]		1			1
X-rays [66]		1			1
Total	0	7	1	7	15

Abbreviations: DPIs, dry-powder inhalers; MMAT, Mixed Methods Appraisal Tool; pMDIs, pressurized metered-dose inhalers.

be 13 000 and 18 000 kt CO_2-eq [52,53], that is, 0.0373% and 0.0517% of total worldwide emissions, respectively (https://ourworldindata.org/CO_2-emissions). Using the EPA Greenhouse Gas Equivalences Calculator [43], the carbon footprint of air traffic in 1 year in Spain is equivalent to 228 years of use of pMDIs. Another interesting comparison is that the amount of pMDIs prescribed in a year in Spain (around 14 million) produces the same amount of CO_2 emissions as all the existing cars in the country for 4 or 5 days. In 2018, the average carbon footprint of a person in 1 year in Spain was 7.15 t CO_2-eq, 18% of which (1.27 t CO_2-eq) was related to transport [54]. Similarly, the impact of petrol cars in Spain was estimated to be 424 g CO_2-eq/passenger/km in 2008 [55]. Consequently, and as previously reported, emissions of HFC propellants account for a small proportion of emissions of high-global-warming-potential gases and are dwarfed by other emissions such as CO_2, nitrous oxide, and methane [18].

Rescue medication for asthma exacerbations, mainly salbutamol and other SABAs, accounts for the vast majority of the overall use of pMDIs [24]. In this work, we simulated a hypothetical switch from all pMDIs to DPIs, except those containing SABAs. In this hypothetical scenario, emissions due to pMDIs would be 146 618.10 t CO_2-eq/year, accounting for 0.0579% of total yearly national CO_2 emissions. Consequently, this change would not even reduce emissions of pMDIs to half the current value. Nevertheless, the proper characterization of the impact of inhalers on climate change should include not only emissions due to propellants, but also the carbon footprint of the whole product life cycle [56]. This includes emissions caused by material acquisition, preprocessing, production, distribution, use, and end of life.

One relevant issue is whether a complete switch from pMDIs to DPIs would be cost-effective or not. In the UK, where pMDIs are used more frequently than in the rest of Europe [57], a study showed that a switch considering the current proportions of brand prescriptions would result in an increase in associated costs [56].

An even more relevant consideration is the impact of changing devices for environmental reasons on clinical outcomes and patient health. The costs associated with switching inhalers for reasons other than clinical reasons could be potentially high for health systems, including a possible risk of loss of asthma control. Under this premise, European and Spanish scientific societies and patient organizations, while committed to achieving more sustainable health care, have opposed switching based exclusively on environmental criteria [23,29-31]. Most of the studies included in this systematic review reported no significant differences or provided no statistically significant results in terms of efficacy, handling, satisfaction, safety, and use of health care resources. Assessment of adherence seemed to favor pMDIs over DPIs, albeit with a low quality of evidence.

In view of these nonconclusive results in terms of clinical outcomes, it is difficult to state how switching inhalers for only environmental reasons could affect the efficacy of treatment in asthma patients. Moreover, a large proportion of asthma patients, including pediatric patients (≤6 years), older patients, and those with low inspiratory flow (≤ 30 L/min), are not candidates for treatment with DPIs [24]. Additionally, rapid relief of symptoms at any therapeutic step, treatment of intermittent asthma, and prevention of bronchoconstriction due to physical exercise need to be managed with SABAs, which are mostly available as pMDIs [24]. While the contribution of pMDIs to global warming is relatively small, it needs to be reduced. In this sense, our thought is

that substantial reductions in the carbon footprint could also be achieved by transitioning to propellants with lower warming potential for pMDIs, such as HFA-152a and HFA-1234ze [58]. However, it should be noted that greening of inhalers comes with a cost: the switch to albuterol inhalers with HFAs instead of CFCs costs payers and patients billions of dollars. Without patent and regulatory reform, a similar pattern could be repeated in some countries and in specific situations [59]. This approach would overcome the substitution of pMDIs with DPIs/SMIs while preserving patient needs, choice, and access to any device, which are essential factors for optimizing both treatment and clinical outcomes [60].

Our first-in-class systematic review was carried out using a strict and exhaustive methodology, with well-defined questions. Moreover, the quality of the studies reviewed was assessed using the MMAT score. Nevertheless, the review has certain limitations. Firstly, data on inhaler sales in Spain used for this study include devices prescribed not only for asthma but also for COPD and other respiratory diseases, indicating that total asthma-related emissions are overestimated for each type of inhaler. Consequently, the current impact on the carbon footprint of pMDIs for asthma treatment is lower than reported here. Secondly, some of the publications included for QUESTION 2 compared devices containing different active ingredients, thus potentially affecting clinical efficacy and safety outcomes; to counteract this limitation, results are also presented in supplementary tables indicating the drugs under study (Supplementary material 13-19). Thirdly, the heterogeneity of clinical outcomes did not allow us to conduct a meta-analysis of the results. There is also a potential language bias, since only publications in English and Spanish were included. Moreover, unpublished studies and studies with no available abstract were excluded. However, it is noteworthy that only 3 publications were eliminated for QUESTION 1 (2 references from PubMed and 1 from Cochrane) and 11 for QUESTION 2 (6 references from PubMed and 5 from Cochrane) on account of this criterion.

Conclusions

Current CO_2 emissions from pMDIs account for a small percentage of the total carbon footprint in Spain, as described in other countries and worldwide. Despite the minimum impact of pMDIs, there is a need for research into new and more sustainable devices with less contaminating propellants. The hypothetical scenario of switching from pMDIs to DPIs excluding SABAs could reduce the carbon footprint of pMDIs. However, since the clinical outcomes were inconclusive, it is challenging to anticipate how switching inhalers for environmental reasons only could affect the efficacy of treatment in asthma patients. Suitability and clinical criteria such as age and inspiratory flow should be prioritized at prescription, and treatment should be individualized. The studies included in this review were from many different countries, and there were no exclusion criteria based on geographical area, patient profile, or device type. Therefore, our conclusions about the clinical impact of an inhaler switch could be generalized.

Acknowledgments

Editorial and medical writing support for the preparation of this manuscript was provided by Adelphi Targis and Jemina Moreto and was funded with an unconditional grant from Chiesi España.

Funding

This review was supported by an unconditional grant from Chiesi Spain, which covered the design of the strategy for the systematic review, its implementation, the analysis of the results, and the editorial support for medical writing.

Conflicts of Interest

Montoro J. has received the following: grants/contracts from Sociedad Española de Alergología e Inmunología Clínica (SEAIC); consulting fees from ALK-Abelló, Astra Zeneca, and Sanofi; speaker fees from AstraZeneca, Chiesi, GSK, Faes, Sanofi, and Novartis.

Antolín-Amérigo D. has received the following: grants/contracts from Sociedad Española de Alergología e Inmunología Clínica (SEAIC); consulting fees from ALK-Abelló, AstraZeneca, Chiesi, and Gebro; speaker fees from AstraZeneca, Chiesi, Gebro, GSK, Leti Pharma, Mundipharma, Novartis, Roxall, and Sanofi.

Izquierdo A. has received the following: grants/contracts from Sociedad Española de Alergología e Inmunología Clínica (SEAIC) and speaker fees from GSK, Sanofi, Novartis, Menarini, Lofarma, Viatris, and Uriach.

Zapata J.J. has received the following: grants/contracts from Sociedad Española de Alergología e Inmunología Clínica (SEAIC); consulting fees from Allergy T and Stallergenes; speaker fees from Astra Zeneca, GSK, Stallergenes, Diater, Leti Pharma, Inmunotek, ALK, Allergy Therapeutics, Thermo Fisher, Asac Pharmaceutical Immunology, Hal Allergy, and Chiesi.

Valero A.L. has received the following: grants/contracts from Sociedad Española de Alergología e Inmunología Clínica (SEAIC); consulting fees from ALK-Abelló, Astra Zeneca, Chiesi, and Gebro; speaker fees from AstraZeneca, Chiesi, Gebro, GSK, Leti Pharma, Mundipharma, Novartis, and Sanofi.

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Manuscript received September 29, 2022; accepted for publication January 3, 2023.

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