The impact of inhalers for asthma on the global climate: a systematic review of carbon footprint and clinical outcomes in Spain

Brief running title: Environmental impact of inhalers

Montoro J[1], Antolín-Amérigo D[2], Izquierdo-Domínguez A[3], Zapata JJ[4], González G[5], Valero A[6]

[1]Sección de Alergia, Unidad Especializada de Asma Grave, Hospital de Líria, Facultad de Medicina, Universidad Católica de Valencia "San Vicente Mártir", Valencia, Spain

[2]Servicio de Alergia, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

[3]Servicio de Alergología, Consorcio Sanitario de Terrassa, Barcelona, España

[4]Clínica de Alergia Dr. Zapata, Almería, Spain

[5]Adelphi Targis, Barcelona, Spain

[6]Servicio de Alergología Hospital Clínic, IDIBAPS, CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain

Corresponding:

Javier Montoro Lacomba M.D., Ph.D.
Allergy Section. Severe Asthma Specialized Unit.
Hospital Arnau de Vilanova-Líria. Valencia.
Department of Medicine. Catholic University of Valencia "San Vicente Mártir".
E-mail: montoro_fra@gva.es

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Abstract

Background: Pressurised metered-dose inhalers (pMDIs) exert some environmental impact due to their effect on CO_2 emissions. There are other therapeutic alternatives with less environmental impact that are being widely used. Nevertheless, the choice of the device and the appropriate therapy should answer 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. Secondly, we aimed to evaluate the potential impact of switching pMDIs to dry-powder inhalers (DPIs) in patients with asthma.

Methods: Systematic review of the evidence published between 2010-2021 was carried out. Average annual CO_2 emissions of DPIs and pMDIs were calculated in two scenarios: present 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 accounts for 0.0056% and 0.0909%, respectively, of total emissions in Spain. In the event of a conversion of all pMDIs to DPIs, except those for rescue medication, these percentages would be 0.0076% and 0.0579%. The evaluation of efficacy, handling, satisfaction, safety and healthcare resources utilization was not conclusive.

Conclusions: Current CO_2 emissions derived from 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 or inspiratory flow should be prioritised at inhaler prescription.

Key words: Asthma. Inhaler devices. Metered-Dose Inhalers. Anti-Asthmatic 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 suffered from asthma in 2019 [2]. In Spain, 5-14% of the population is affected by asthma [3] and 1,134 deaths were attributable to this disease in 2015 [4]. Inhalation is the main and most frequent method of administration of the drugs used for asthma treatment [1]. Several types of devices for inhaled therapy coexist on the market: pressurised metered-dose inhalers (pMDIs); dry-powder inhalers (DPIs); liquid multi-dose spray devices, such as soft mist inhalers (SMIs); nebulizers; and spacer chambers. The prescription patterns of inhalers for any disease are different across Europe [5], although pMDIs, which are used worldwide, are the most prescribed inhalers [6]. In Spain, some 30 million inhalers were consumed in 2020, 48% of which were pMDIs, 45% DPIs and 7% SMIs [7,8]. Each type of inhaler delivers advantages and disadvantages in terms of portability, ease and speed of use and cost [9–11]. Although only observational studies have shown a correlation between patient satisfaction with adherence and disease control [12,13], it is important to guarantee patient satisfaction with the selected devices. Moreover, poor therapy adherence is traditionally high in patients with asthma [14] and has a negative impact on disease control [15,16].

Beyond the improvement of the clinical outcomes obtained with different types of inhalers, their potential impact on CO_2 emissions and the environment is currently being debated. Historically, pMDIs contained chlorofluorocarbon (CFCs) propellants. CFCs were banned following the Montreal Protocol of 1987 - which took effect in 1989 - due 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, the EU Regulation (517/2014) provides for the reduction of fluorinated gases due 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 the access to patients to the 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, only, when patients' characteristics are appropriate [21,22], although they have also underlined that a switch of inhalation devices due to environmental reasons could have health and economic consequences [23]. Additionally, the current Spanish guideline GEMA 5.2 state that changes of inhaler for non-clinical reasons could lead to a risk of poorer adherence and a worsening of symptoms [24]. The GOLD 2023 international guidelines on Chronic Obstructive Pulmonary Disease (COPD) management 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 combination as rescue medication and highlights the risk of the excessive use of SABA with respect to

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exacerbations [1]. Reality is far from what GINA recommends and approximately one-third of asthma patients in Spain are prescribed three or more SABA canisters per year [26], with the resulting economic and environmental consequences [27,28].

In May 2021, the European Respiratory Society (ERS) 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 each patient with asthma [29]. Patient organisations have also taken a stand on the matter [30,31].

As reported in several studies, the environmental impact of inhalers is different for each specific product. We hypothesised 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, our approach was intended (1) to estimate the impact of pMDIs on CO_2 emissions in Spain and (2) to evaluate the potential impact of switching prescriptions of pMDIs to DPIs in patients with asthma following exclusively environmental criteria. Nebulizers have not been considered for this work due to their residual current use; 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 two independent experts in the methodology used for this research (Gloria González and Sara García). The entire process was supervised and reviewed by the rest of the authors of this publication. Two research questions were formulated, the second one following the PICO (Patient, Intervention, Comparison, Outcome) method [32]:

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

Search strategy

Several preliminary search strategies, including different keywords 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 any filter. The search was performed within predefined time limits from 2010 to 2021, as throughout this time frame the importance of the carbon footprint has begun to be emphasized. A total of 24 randomized clinical trials published prior to 2010 were also reviewed; half of them analysed the equivalence/non-inferiority 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 efficacy and safety of various types of pMDI, patient adherence and perception, 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 also reviewed; those published within the predefined time limits were also included in the analysis. Following

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the removal of duplicates, all the publications were screened by title and abstract, and the selection criteria were checked by two reviewers.

Selection of publications and data collection

Publications in languages other than English or Spanish were identified but appear as excluded in 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. The two reviewers extracted the data that provided information to answer the research questions on a standardised sheet that included study characteristics, evaluation variables and results. A preliminary extraction of information from three studies was carried out by the two reviewers and was compared to check consistency. A third reviewer checked a random sample of 15% of the records and also 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

No confounding assessment was performed, although characteristics that were potentially confounding variables were collected 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 two independent reviewers using the Mixed Methods Evaluation Tool (MMAT) [39]. Publications with 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 the publications with MMAT score > 60.

Analysis

Data regarding the carbon footprintof DPIs and pMDIs were found in publications in a heterogeneous presentation and the units were homogenised. For two publications showing carbon footprint per dose, the data were recalculated to CF per pack [40,41]. The number of doses per pack was obtained from the Online Centre of Information of Authorised Medicines of the Spanish Agency of Medicines and Medical Devices [42]. The data 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 CF 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 two scenarios: 1) The present situation: considering current data on DPI and pMDI units sold in 2020, and 2) Hypothetical situation: considering a potential switch of all pMDIs sold in 2020 to DPIs, with the exception of those containing short-acting beta-2 agonists (SABA), that suppose the most prescribed pMDIs in Spain, as a rescue medication, and are the largest contributors to global emissions out of total pMDI devices. This exception was done since pMDIs containing SABA are commonly used as rescue medication by asthma patients and are, therefore, more difficult to replace.

Given the great heterogeneity of outcomes found for QUESTION 2, the results with statistical significance (p value <0.05) were counted as significant for any of the options (DPIs or pMDIs) and those without statistical significance (p value >0.05) as non-significant. In publications with

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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 favouring DPIs or pMDIs were summated.

Results

Overview of included studies

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 four after full-text screening. A total of 11 publications were considered and eight were included in the analysis. The other three 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 summarises the characteristics and the results of each publication on the treatment of asthma reporting the inhaler-derived carbon footprint. Supplementary material 5 summarises the characteristics of each publication 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 1,241.79 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 x 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 SABA, was simulated. A total amount 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, respectively, accounting for 0.0579% and 0.0076% of total emissions (Table 1).

Impact of the inhaler on clinical outcomes

Efficacy

A total of 26 reviewed publications addressed the efficacy of pMDIs and/or DPIs. Of these, 21 addressed asthma control (asthma control, exacerbations, hospitalisation 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 use-free days, awakening-free nights, Asthma Control Test – ACT - score, Asthma Control Questionnaire – ACQ - score, daytime symptoms score, night-time symptoms score, wheezing score, accessory muscle score, asthma control score, caregiver assessment, physician

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assessment, risk domain asthma control, Borg dyspnoea 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 or lung function); one addressed duration of response and one addressed time to response.

A pool of 21 publications presented an MMAT score >60. Of a total of 189 efficacy units found in them, 112 did not show significant differences, 52 favoured pMDIs, and five favoured DPIs. Thirty-one asthma control units did not show significant differences, 30 favoured pMDIs, and one favoured DPIs. Eighty lung function units did not show significant differences, 22 favoured pMDIs, and four favoured DPIs. No duration of response or time to response unit favoured either DPIs or pMDIs (Table 2, Figure 2).

After the sensitivity analysis, including all publications regardless of their MMAT score, 130 efficacy units did not show significant differences, 56 favoured pMDIs and five favoured DPIs (Supplementary material 6). Results according to the molecules 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 or the Asthma Health Questionnaire (AHQ)-33-Japan score.

Only one publication presented an MMAT score >60 [44], and the two quality of life units found favoured pMDIs.

After the sensitivity analysis, including all the publications regardless of their MMAT score, two quality of life units favoured pMDIs, one did not show significant differences, and none favoured DPIs (Supplementary material 7). Results according to the molecules 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 or patients requiring instructions.

Seven publications presented an MMAT score >60, and of 13 handling units found in them, five did not show significant differences, three favoured DPIs and three favoured pMDIs (Table 3, Figure 2).

After the sensitivity analysis, including all the publications regardless of their MMAT score, eleven handling units did not show significant differences, five favoured DPIs and five favoured pMDIs (Supplementary material 8). Results according to the molecules 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 (MAQ) score,

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compliance, changes in therapy, <50% adherence, persistence, duration of treatment or treatment possession.

Six publications presented an MMAT score >60. Nine adherence units were found in them, six favoured pMDIs, two did not show significant differences, and one favoured DPIs (Table 4, Figure 2).

After the sensitivity analysis, including all the publications regardless of their MMAT score, six adherence units favoured pMDIs, three did not show significant differences, and one favoured DPIs (Supplementary material 9). Results according to the molecules 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 (TSQM) score, asthma knowledge questionnaire for consumers (CQ) score, patient satisfaction questionnaire, Asthma Treatment Satisfaction Measure (ATSM) score, or preference.

Three publications presented an MMAT score >60 [45–47]. Five satisfaction units were found in them; three did not show significant differences, two favoured pMDIs and none favoured DPIs.

After the sensitivity analysis, including all the publications regardless of their MMAT score, five satisfaction units did not show significant differences, three favoured pMDIs, and none favoured DPIs (Supplementary material 10). Results according to the molecules 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 seven publications with MMAT >60, seventeen did not show significant differences, and none favoured either DPIs or pMDIs (Table 6).

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

Use of healthcare resources

Three publications addressed the use of healthcare 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 doctor, unscheduled doctor visit, complementary tests, days off work, in-hospital visit, hospital admissions, hospitalisation days, laboratory tests, visits to family doctor or X-rays.

All three publications presented an MMAT score >60. Fifteen units regarding the use of healthcare resources were found, seven did not show significant differences, seven favoured pMDIs, and none favoured DPIs (Table 5, Figure 2). Results according to the molecules used in each publication are also shown in Supplementary material 19.

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Discussion

This work includes a review of the scientific evidence on CO_2 emissions from pMDIs, SMIs and DPIs used to treat asthma, as well as the impact of a hypothetical switch from pMDIs to DPIs on clinical outcomes. A contribution of 0.0909% of total CO_2 emissions per year has been estimated in Spain in the case of pMDIs. In the United Kingdom, where the use of pMDI is higher (both in proportion to DPI and in absolute values) than in Spain [48], emissions due to pMDIs account for 0.1% of the total national and 3.1% of the NHS carbon footprint. respectively [49,50]. In the United States the discharge and leakage of hydrofluoroalkanes (HFAs) from pMDIs has been described to generate 2,500 kt CO_2-eq [51]. Worldwide emissions due to pMDIs have been reported as 13,000 and 18,000 kt CO_2-eq in different works [52,53], which respectively represent 0.0373% and 0.0517% of total worldwide emissions (https://ourworldindata.org/co2-emissions). Using the EPA Greenhouse Gas Equivalences Calculator [43], the carbon footprint of air traffic in one 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 four or five days. In 2018, the average carbon footprint of a person in one year in Spain was 7.15 tCO_2-eq, 18% of which 1.27 tCO_2-eq was related to transport [54]. Similarly, the impact of petrol cars in Spain was estimated to be 424g. 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 SABA, accounts for the vast majority of the overall use of pMDIs [24]. In this work, a hypothetical situation of a switch from all pMDIs to DPIs except those containing SABA was simulated. In this hypothetical scenario, emissions due to pMDIs would be 146,618.10 t of CO2-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 characterisation 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, pre-processing, 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 the use of pMDIs is higher compared to 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 a switch of inhaler without 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 organisations, although being committed with a change towards a more sustainable healthcare, have opposed this switch on the strength of exclusively environmental criteria [23,29–31]. In the majority of studies included in this systematic review, no significant differences are shown or statistical significance was not provided in terms of efficacy, handling, satisfaction, safety and healthcare resources utilization outcomes. Adherence assessment seemed to favour pMDIs compared to DPIs, with low quality of evidence.

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In view of these non-conclusive results in terms of clinical outcomes it is difficult to state how the change of inhaler only due to environmental reasons could affect the efficacy of treatment in those patients affected by asthma. Moreover, a large proportion of patients with asthma, such as paediatric (≤ 6 years old) or elderly patients and those with low inspiratory flow (≤ 30 l/min), are not candidates for the treatment with DPIs [24]. Additionally, the rapid relief of symptoms at any therapeutic step, the treatment of intermittent asthma, and the prevention of bronchoconstriction due to physical exercise need to be addressed with SABA, which are mostly available with pMDIs [24]. Albeit 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 CO_2 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 HFA instead of CFCs cost payers and patients billions of dollars. Without patent and regulatory reform, this pattern could be repeated in some countries or particular situations [59]. This approach would overcome the substitution of pMDIs for DPIs/SMIs while preserving patient needs, choice and access to any device, which are essential factors for optimizing the treatment and the clinical outcomes [60].

This systematic review was carried out using a strict and exhaustive methodology, with well-defined questions and is first-in-class. Moreover, the quality of the studies reviewed was assessed using MMAT. Nevertheless, this review has certain limitations. Firstly, the data about inhaler sales in Spain used for this study include devices prescribed not only for asthma but also for COPD and other respiratory diseases, which means 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 what is reported here. Secondly, some of the publications included for QUESTION 2 compared devices containing different active ingredients, which could affect clinical efficacy or safety outcomes; to counteract this limitation, results have also been presented in supplemental tables indicating the molecules in study (Supplemental material 13-19). Thirdly, the heterogeneity of clinical outcomes did not allow us to conduct a typical meta-analytic combination of 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 should be taken into account that only three publications were eliminated for QUESTION 1 (two references from PubMed® and one from Cochrane) and 11 for QUESTION 2 (six references from PubMed® and five from Cochrane) on account of this criterion.

Conclusions

Current CO_2 emissions derived from pMDIs account for a small percentage of the total carbon footprint in Spain, just like it has been 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 pMDI to DPI excluding SABA could reduce the carbon footprint of pMDIs. However, since the clinical outcomes were inconclusive, it is challenging to anticipate how the change of inhaler only due to environmental reasons could affect the efficacy of treatment in those patients affected by asthma. Suitability and clinical criteria such as age or inspiratory flow should be prioritised at prescription and treatment individualised. The studies included in this review were originated from many different countries and there were no exclusion criteria due to geographical area,

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patient profiles or device type. Therefore, our conclusions about the clinical impact of an inhaler switch could be mainstreamed.

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Conflicts of interest

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

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

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

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

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Tables

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*	
	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**	0.0056%	0.0909%	0.0076%	0.0579%

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

* Conversion of all pMDIs sold in Spain in 2020 to DPIs, except packs that correspond to SABA.

** Global greenhouse gas emissions were calculated using the annual values from 2016 to 2020 in Spain (https://ourworldindata.org/co2-emissions) and the mean value was 2.53×10^{11} kg.

Table 2. Efficacy outcomes according to the type of inhaler in publications with MMAT >60.

Endpoint (publication)	Favouring DPIs	Favouring 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**

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

Table 3. Handling outcomes according to the type of inhaler in publications with MMAT >60.

Endpoint (publication)	Favouring DPIs	Favouring pMDIs	Undetermined	Not significant	Total
Correct technique [46] [70] [78]		**2**	**1**	**1**	**4**
Critical errors [79]				**1**	**1**
Easiness 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**

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

Table 4. Adherence outcomes according to the type of inhaler in publications with MMAT >60.

Publication	Favouring DPIs	Favouring 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**

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

Table 5. Use of healthcare resources outcomes according to the type of inhaler in publications with MMAT >60.

Endpoint (publication)	Favouring DPIs	Favouring 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
Hospitalisation days [66]		1			1
Laboratory tests [66]		1			1
Phone calls to doctor [44]				1	1
Unscheduled doctor visit [44]				1	1
Visits to emergency room [44] [66] [70]		2	**1**		3
Visits to family doctor [66]		1			1
X-rays [66]		1			1
Total	**0**	**7**	**1**	**7**	**15**

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

Table 6. Safety outcomes according to the type of inhaler in publications with MMAT >60.

Endpoint (publication)	Favouring DPIs	Favouring pMDIs	Undetermined	Not significant	Total
Bronchitis [70]				1	1
Cold [63]				1	1
Dyspnoea [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**

DPIs, dry-powder inhalers; pMDIs, pressurised metered-dose inhalers

Figures

Figure 1. PRISMA flowchart.

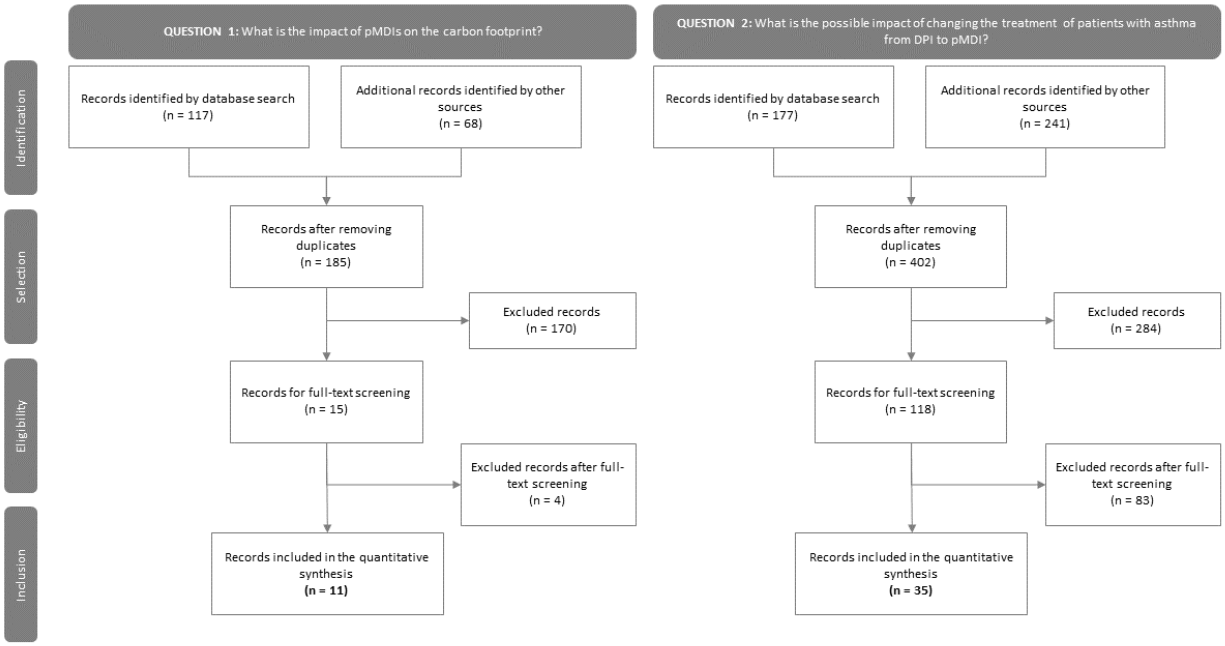

Figure 2. Percentage of outcomes favouring each type of inhaler, with undetermined or with non-significant result in publications with MMAT >60.