Andrzej Emeryk[1], Tomasz R Sosnowski[2], Maciej Kupczyk[3], Paweł Śliwiński[4], Justyna Zajdel-Całkowska[5,6], Tadeusz M Zielonka[7], Agnieszka Mastalerz-Migas[8]

[1]Department of Paediatric Pulmonology and Rheumatology, Medical University of Lublin, Lublin, Poland
[2]Chair of Integrated Process Engineering, Faculty of Chemical and Process Engineering, Warsaw University of Technology, Warsaw, Poland
[3]Department of Internal Medicine, Asthma and Allergy, Norbert Barlicki Memorial Teaching Hospital No. 1 of the Medical University of Lodz, Lodz, Poland
[4]2nd Department of Respiratory Medicine, Institute of Tuberculosis and Lung Diseases, Warsaw, Poland
[5]Faculty of Law and Administration, Lazarski University in Warsaw, Warsaw, Poland
[6]Chair of Humanities, Faculty of Health Sciences, Medical University of Lodz, Lodz, Poland
[7]Chair and Department of Family Medicine, Faculty of Medicine, Medical University of Warsaw, Warsaw, Poland
[8]Department of Family Medicine, Wroclaw Medical University, Wroclaw, Poland

Impact of inhalers used in the treatment of respiratory diseases on global warming

Abstract

The term "carbon footprint" describes the emission of greenhouse gases into the environment as a result of human activities. The healthcare sector is responsible for 5–8% of the value of global greenhouse gas emissions, of which medical aerosols account for only 0.03% of the total emissions. The reduction of greenhouse gases, including those used for the production and use of medicinal products and medical devices, is part of the responsibilities that Poland and the respective countries should undertake in order to implement the assumptions of international law. At the level of medical law, this obligation correlates with the need to exercise due diligence in the process of providing health services, including the selection of low-emission medical products and devices (inhalers) and providing patients with information on how to handle used products and devices, with particular emphasis on those that imply greenhouse gas emissions. Pressurized metered dose inhalers (pMDI) containing the hydrofluoroalkane 134a demonstrate the largest carbon footprint, followed by a metered dose liquid inhaler and dry powder inhalers (DPI). The carbon footprint of DPI with a given drug is 13–32 times lower than it is in the case of the corresponding pMDI. Replacement of pMDI by DPI is one of the effective methods to reduce the carbon footprint of inhalers, and the replacement should be based on current medical knowledge. A recycling system for all types of inhalers must be urgently implemented.

Key words: carbon footprint, global warming potential, pressurized metered dose inhaler, hydrofluoroalkane, dry powder inhaler, inhalation therapy

Adv Respir Med. 2021; 89: 427–438

Introduction

The aim of the publication was to present the influence of inhalers used in the treatment of respiratory diseases on global warming. For this purpose, the literature available in the PubMed database was reviewed. Data provided by inhaler manufacturers were also used. The following parts of the article present the definitions and indicators of the carbon footprint, European and Polish legal regulations on the reduction of greenhouse gases, a short review of inhalers and inhalation drugs based on the example of the Polish market. Further section presents the results of studies on the carbon footprint of selected inhalers and methods of reducing the negative impact of inhalers on the environment, including the problem of replacing pressurized metered dose inhaler (pMDI) with dry powder inhaler (DPI).

Address for correspondence: Andrzej Emeryk, Department of Pediatric Pulmonology and Rheumatology Medical University in Lublin, Lublin, Poland; e-mail: andrzejemeryk@gmail.com

DOI: 10.5603/ARM.a2021.0092 | Received: 16.03.2021 | | ISSN 2451–4934 | e-ISSN 2543–6031

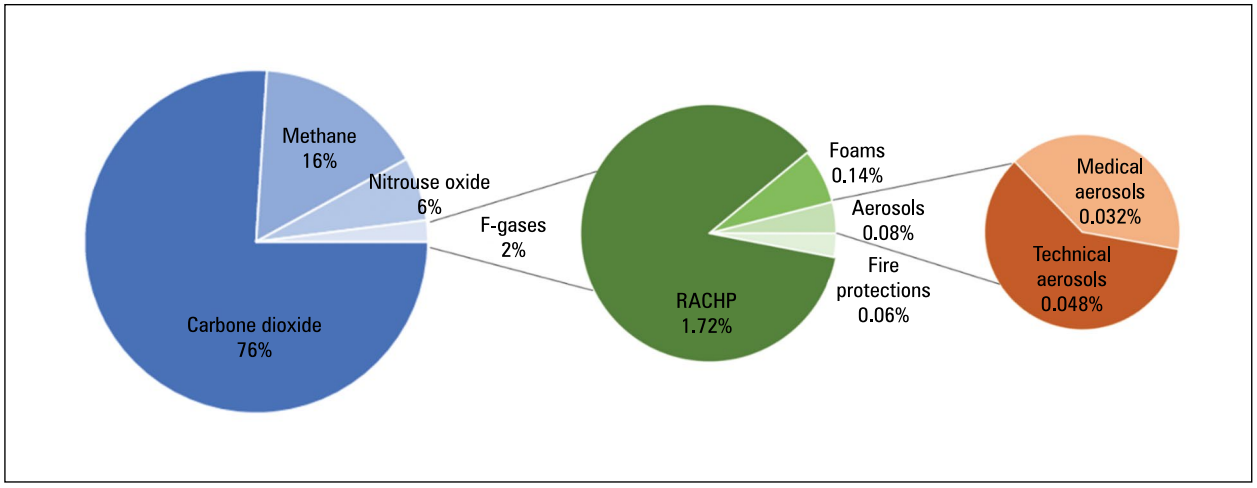

Figure 1. The share of medical aerosols in the total GHG pool in the world in 2016 [7]. RACHP — Refrigeration, Air-Conditioning, Heat Pomp

Basic definitions and indicators of the carbon footprint

Term carbon footprint describes the emission of greenhouse gases (GHG), that are generated to the environment due to human activity [1]. Carbon footprint is quantified by the global warming potential (GWP), expressed in tones, kilograms or grams of the equivalent emitted carbon dioxide (CO_2): t CO_2e, kg CO_2e or g CO_2e. GWP shows how many times the impact of a single t/kg/g of a given gas emitted to the atmosphere is higher that the greenhouse effect caused by a single t/kg/g of CO_2. For instance, GWP values for methane and hydrofluoroalkane (HFA) 134a are 23 and 1300 t CO_2e, respectively [2]. Accordingly, one tone of emitted methane causes the same effect as 23 tones of emitted CO_2, while one tone of HFA 134a — as 1300 tones of emitted CO_2. Another important indicator of the impact of GHG on the natural environment is their atmospheric persistence (stability). Methane is stable in the atmosphere for 12–15 years, whereas various HFAs — above 250 years. The stability of sulfur hexafluoride (SF6) in the atmosphere is up to 3200 years [3]. Among GHGs that are defined as natural or anthropogenic components of the atmosphere that absorb and reemit infrared radiation, we can find CO_2, CH_4, N_2O and many gases that contain fluoride (the F-gases), including: SF6, perfluorocarbons (PFCs), chloroflourocarbons (CFCs, including freons) and hydrofluorocarbons (HFCs, including HFAs). HFCs that are used in pressurized metered dose inhalers (pMDIs) are mainly HFA 134a and HFA P277 [4].

Power industry and transportation are the predominant sources of GHGs on the global scale, where CO_2 forms ¾ of the total emission. According to the available data in 2016, the global emission of CO_2 was above 34 bln tones. Different regions and countries have various input to this emission. China, USA, India and Russia are dominating being responsible for 55% of global CO_2 emission. Accoring to the same data, the input of Poland is only 0.83% of global emission of CO_2 [5]. It is also known that F-gases compose 2% of global GHG emission and they are primarily used in cooling and refrigeration, AC systems and fire fighting [6]. Only 0.03% of total GHG emission is related to medical aerosols [7] (Figure 1).

The broadly understood healthcare sector is responsible for 5–8% of the global GHG emission value [8]. In Germany, 7% of the country's carbon footprint is produced in the health sector [9]. It is not known how big this share is in Poland. Among the many elements that make up this value, inhalers, especially pMDI, occupy a certain proportion. Over 800 million HFA-based pMDIs are sold annually worldwide (> 11,500 tones/year), resulting in an estimated CO_2e of > 13 million tonnes [10, 11]. In light of the above, global and regional non-governmental organizations and governments of several countries have started implementing projects aimed at reducing GHG emissions from the healthcare sector [12]. A policy of pro-ecological public procurement is proposed and the inclusion of these considerations in the decision-making process on purchasing and financing medical technologies. Reducing CO_2 production has become the goal of the sustainable development of pharmaceutical companies. In a more patient-centered healthcare ecosystem, patients are increasingly acting as consumers and

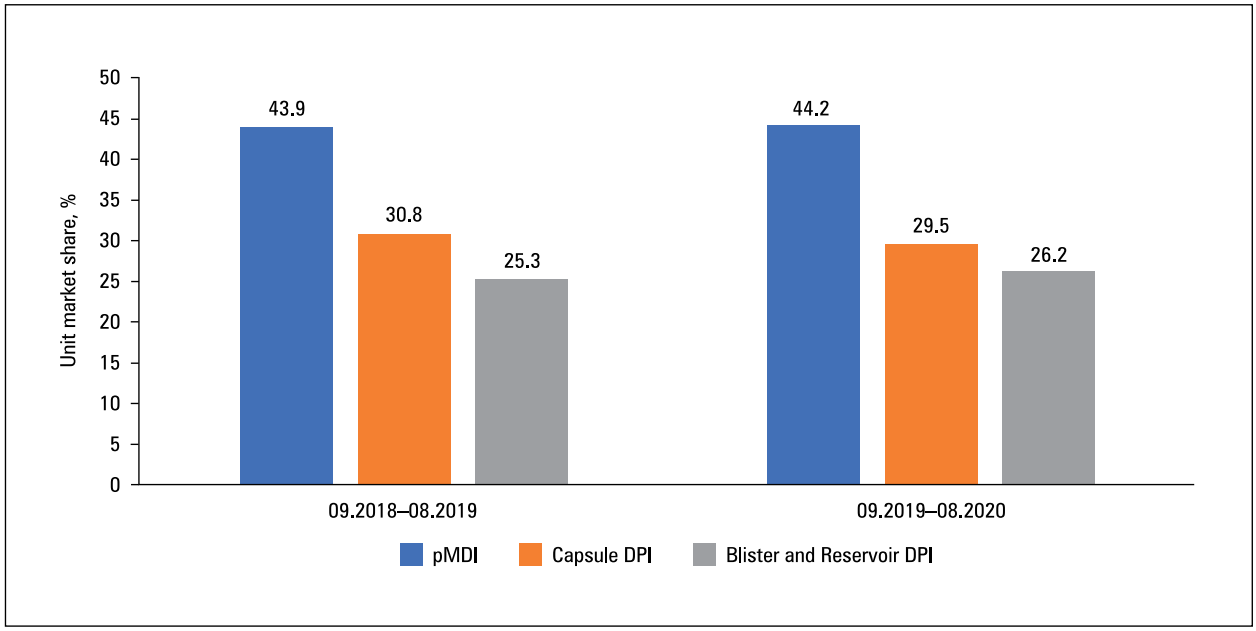

Figure 2. Sale of pMDI and DPI inhalers to pharmacies in 12-month periods from 09.2018 to 08.2019 and from 09.2019 to 08.2020 (data from the Pharmaceutical Database, IQVIA 08/2020 sell in.). DPI — dry powder inhaler; pMDI — pressurized metered dose inhaler

Table 1. Availability of inhaled drugs in Poland in the respective types of inhalers (as of 01/01/2021)

Inhaler/Drug	ICS	LABA	ICS + LABA	SABA	SAMA	SABA + SAMA	LAMA	LABA + LAMA	ICS + LABA + LAMA
pMDI	+	+	+	+	+	+	–	–	–
pMDI-BA	+	–	–	–	–	–	–	–	–
DPIs	+	+	+	+	–	–	+	+	+
Nebulizer	+	+	–	+	+	+	–	–	–

DPIs — dry powder inhalers; ICS — inhaled corticosteroid; LABA — long acting beta-2 agonist; LAMA — long acting anti-muscarinic agent; pMDI — pressurized metered dose inhaler; pMDI-BA — pressurized metered dose inhaler-breath actuated; SABA — short acting beta-2 agonist; SAMA — short acting anti-muscarinic agent

may prefer environmentally friendly products (including inhalers) [13].

Review of inhalers and inhalation drugs on the example of the Polish market

The inhalation route is the most important method to administer majority of drugs used in asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis and other acute or chronic respiratory diseases [14–16]. Aerosol therapy can be carried out with several groups of inhalation devices (inhalers), such as:

— pressurized metered dose inhaler (pMDI) with its variant — a pressurized metered dose inhaler — breath actuated — pMDI-BA;
— dry powder inhaler (DPI) — a lot of different types (generations) of inhalers;
— metered dose liquid inhaler (MDLI) — one inhaler on the market in the country;
— nebulizers (pneumatic and ultrasonic, including mesh nebulizers) — a lot of devices that are technically very diverse.

There is huge variation between the respective countries in the share of inhalers being used. For example, in 2011 in Sweden, about 90% of inhaled corticosteroids (ICS) were inhaled using DPI, while in the UK about 80% were inhaled using pMDI [17]. The share of individual types of inhalers in the Polish market is shown in Figure 2.

The data contained in the BAZYL Pharmaceutical Database, which are partially presented in Figure 2, show that a little over 13 million pMDI and DPI packages are sold in Poland per year. Of these, pMDI accounts for approx. 44%, single-dose capsule DPIs for approx. 30%, and multi-dose blister and reservoir DPIs for approx. 26% of this market. The list does not include MDLI (Respimat) and nebuliser devices.

Table 2. Medicines registered in Poland in the respective types of DPI (as of 01/10/2020)

Inhaler's trade name	DPI type	Medicines available
Aerolizer®	Capsule	Budesonide, formoterol
CNG Fantasmino®	Capsule	Budesonide, fluticasone propionate, formoterol, salmeterol
CNG Breezhaler®*	Capsule	Budesonide, mometazon/indacaterol, indacaterol/glycopyrronium, mometazon/indacaterol/glycopyrronium
Diskus®*	Blister	Fluticasone propionate, salbutamol, salmeterol, fluticasone propionate/salmeterol
Generic Diskus (Aerostar®, G7)	Blister	Fluticasone propionate/salmeterol
Easyhaler®	Reservoir	Budezonid, salbutamol, formoterol, budezonid/formoterol
Ellipta®*	Blister	Umeclidinium, fluticasone furoate/vilanterol, umeclidinium/vilanterol, Umeclidinium/fluticasone furoate/vilanterol
Forspiro®	Blister	Fluticasone propionate/salmeterol, budezonid/formoterol
Genuair®	Reservoir	Umeclidinium, Umeclidinium/formoterol
Handihaler®	Capsule	Tiotropium
Nexthaler®	Reservoir	Beklometazone/formoterol
Novolizer®	Reservoir	Budesonide, salbutamol, formoterol
Podhaler®	Capsule	Tobramycin
Spiromax®*	Reservoir**	Budesonide/formoterol
Turbuhaler®*	Reservoir	Budesonide, formoterol, Budesonide/formoterol
Twisthaler®	Reservoir	Mometasone
Zonda®	Capsule	Tiotropium

*Inhalers also available in an electronic version (sensor recording the use of an inhaler and/or measuring the inspiratory flow), but currently not available in Poland.
**Spiromax® — multidose, reservoir, III generation.
DPI — dry powder inhaler

Table 1 presents various inhaled medications used in the treatment of asthma or COPD available on the Polish market in each type of inhaler, and Table 2 presents the drugs registered in Poland in each DPI.

The wide variety of DPIs is, on the one hand, a good solution for patients and doctors, as it allows individual selection of the appropriate inhaler. However, on the other hand, it causes difficulties in choosing DPI and the need to educate medical personnel and patients. Choosing the right inhaler for a given patient depends on many elements and it is subject to established rules depending on the type of the disease (asthma *vs* COPD *vs* cystic fibrosis), age of patients (children *vs* adults), and other variables, not only clinical [14–19].

European and Polish legislation on greenhouse gas reduction

The issues of reducing GHG are regulated both under European and Polish law. The preamble to the United Nations Framework Convention already States that climate change and its negative effects are one of the key problems facing humanity [20]. It was noted that the highly developed countries have the largest share of global GHG emissions. The purpose of this Convention is, in accordance with the wording of Article 2 thereof, to "achieve (…) stabilization of greenhouse gas concentrations in the atmosphere at a level that would prevent dangerous anthropogenic interference with the climate system (…)" [20]. Another important legal step was the Kyoto Protocol of 11.12.1997, which required 38 developed countries to reduce GHG emissions [21, 22].

On 12 December 2015 in Paris, at the Conference of the Parties to the United Nations Framework Convention on Climate change, 195 States adopted the text of the new climate agreement, the Paris Agreement signed in New York on 22 April 2016, which became applicable at the beginning of 2020, Replacing the Kyoto Protocol [23]. The agreement imposes an obligation on individual States to take two types of action: To reduce CO_2 emissions and to extend their absorption, inter alia, by increasing forestation. In accordance with Article 4 of that Agreement, the reduction of CO_2 emissions is to be achieved as soon as possi-

ble. Individual States are required to identify their contributions (Intended Nationally Determined Contributions) to the fight against climate change and to gradually increase it.

Further legislation relevant to this issue concerns the protection of the ozone layer of the atmosphere. These include Regulations (EC) No 1005/2009 of the European Parliament and of the Council [24] and No 517/2014 [25]. In view of the direct effectiveness of EU regulations, national legislation on this issue is complementary and implementing to EU law, and is intended primarily to enable the latter to be properly applied.

National legislation on the protection of the ozone layer is in force under the Act of 15 may 2015 on substances that deplete the ozone layer and on certain fluorinated greenhouse gases (F-gases) [26]. The provisions of Regulation (EU) NO 517/2014 of the European Parliament and of the Council on fluorinated greenhouse gases regulate environmental issues by reducing emissions of such gases [27].

The first important international document which directly referred to ozone-depleting substances was the Montreal Protocol of 16 September 1987 [26]. The Protocol was amended by an amendment from Kigali of 15 October 2016 [28], which was ratified by Poland on the basis of Article 89(1) of the RP Constitution [29]. On 18 December 2018, the Law of 9 November 2018 on the ratification of the amendments to the Montreal Protocol [30] entered into force. The first result of the adoption of the Kigali amendment is:

1. Extension of the list of controlled substances to 19 HFC substances commonly used as substitutes for ozone-depleting substances but to be GHG with very high GWP values;
2. Introducing a timetable for reducing HFCs, which is separate for developed and developing countries;
3. Extension of the obligation to submit annual reports on HFC production, import and export [31];
4. Extension of the obligation to license imports and exports to HFC;
5. Extending the withdrawal of HFCs in developing countries to the multilateral Fund Protocol funding scheme.

According to Article 4 of the Act on the professions of doctor and dental practitioner, 'a doctor is required to practice the profession, as indicated by current medical knowledge, by the methods and means available to him to prevent, recognize and treat diseases, in accordance with the principles of professional ethics and due diligence' [32]. Due diligence in the treatment process should be understood, inter alia, to eliminate activities which involve the risk of adverse effects for the person being treated or for the general public (even after many years). The use of ecological inhalers prevents distant effects in the area of climate change, which has a direct impact on improving quality of life and health protection. An example of a lack of due diligence can be the choice and use of medicinal products with negative environmental consequences. It should be noted that where the patient declares that he is only in agreement with the handling of non-organic products that are still in circulation, the doctor cannot implement a treatment contrary to the patient's will, even if it considers it to be the optimal way of medical treatment.

In analysing the context of due diligence in the area of GHG reduction, attention should be paid, inter alia, to the British Thoracic Society guidelines, which stress the importance of selecting DPI as an alternative to pMDI, and to informing patients about the possibility of low-carbon inhalation therapy [33]. At the same time, the above-mentioned guidelines emphasize the need to inform patients that optimizing the use of medicinal products involves the use of existing products and also the proper segregation of used packaging of medicinal products.

The last of the topics discussed is important under Polish law. According to it, the packaging of used, expired or damaged medicinal products or medical devices (including inhalers) should be placed in labelled containers, which may be placed, inter alia, in publicly available pharmacies [34]. In the context of the due diligence to which the doctor is responsible, it should be noted that it will inevitably be an element of informing the patient about the handling of used packaging of medicinal products and medical devices (including inhalers), which should be properly disposed of due to the loss of therapeutic value.

In conclusion, the reduction of greenhouse gases, including those used in the manufacture and use of medicinal products and medical devices, falls within the scope of the obligations which Poland and the individual countries should undertake to implement the principles of international law. At the level of medical law, this obligation implies due diligence in the process of providing health services, including the selection of low-carbon products and products (inhalers), and information to patients on how to deal with used products and products, with particular

attention to those which imply greenhouse gas emissions.

Carbon footprint of selected inhalers

In the analysis of the carbon footprint of a given product, including an inhaler, its full "life" cycle should be considered — from its production, through its use, to the disposal of its waste [35]. Comprehensive analysis is possible with the use of a special LCA methodology — life cycle analysis [36, 37]. In order to perform this analysis in relation to medical inhalers, complete information is required about each stage of the process:

1. Manufacturing of the inhaler;
2. Manufacturing of the drug contained therein (that usually includes a proprietary know-how);
3. Distribution and sales channels as well as warehousing of the inhaler;
4. Use of the drug;
5. Maintaining hygiene of the inhaler;
6. Managing (partial or complete) waste of the inhaler and the drug.

For each of these "life" stages of the inhaler, the carbon footprint would have to be determined separately in terms of GWP values (e.g., per delivered dose of the drug or per 100 doses) and then summed up. Accurate data on this subject is not available for many inhalers, making it difficult to reliably quantify and compare inhalation products in terms of their carbon footprint.

The study by Goulet *et al.* [36] is an example of an analysis of the carbon footprint for various inhalers. The authors attempted to compare the carbon footprint of two types of inhalers: pMDI HFA 134a with albuterol 200 μg/dose (Proventil, Merk & Co., Inc., Kenilworth, NJ, USA) and the DeVillbis Pulmo-Aide continuous pneumatic nebulizer (DeVilbiss, Port Washington, NY, USA) using the standard dose of 3 mg of albuterol. In the case of pMDI, the authors analyzed not only the HFA 134a carrier released into the atmosphere during drug administration, but also other components of the inhaler, including an aluminum drug container (canister), dosing valve or polypropylene inhaler housing, carrying a specific carbon footprint. The pneumatic nebulizer, although it does not emit greenhouse gases directly when inhaling the drug, is electrically powered, and consists of many metal and plastic elements that relate to carbon footprint. Even the washing method (by hand or in the dishwasher) and the possible sterilization of the nebulization chamber also contribute to the carbon footprint. The authors cited above showed that the carbon footprint of pMDI HFA 134a is two to three times higher than the carbon footprint of the nebulizer (per dose), the difference is mainly caused by the emission of HFA, a gas with a high GWP value. In the case of a nebulizer, its carbon footprint is significantly influenced by the method of washing the nebulization chamber and mouthpiece — the GWP significantly increases in the case of manual washing. The contribution of other factors, due to the long time of using the device (compressor, nebulization chamber, connecting tubes), remains at a very low level. The authors omitted the issue of the carbon footprint resulting from the management of the used pMDI inhaler and the complete nebulizer, and did not consider the inhalation filter in the nebulizer. Similarly, they considered the contribution of the transport of both inhalers to the carbon footprint to be insignificant. There are no data available on the carbon footprint of mesh nebulizers, although theoretical considerations may indicate lower GWP values vs pneumatic nebulizers (in-house data, unpublished). Another study showed that a GWP of Atrovent pMDI HFA 134a is approx. 14.6 kg CO_2e, and a GWP of Berodual™ pMDI HFA 134a is approx. 16.5 kg CO_2e and these values are approx. 20 times higher than those obtained for drugs administered with MDLI such as Spiriva Respimat® or Berodual Respimat® preparations – both approx. 0.78 kg of CO_2e [38]. In the case of MDLI of the Respimat type, depending on the number of uses (refillable cartridge), the inhaler "produces" between 0.77 and 1.03 kg of CO_2 [39]. In pMDI, more than 95% of GWP comes from the HFA carrier, and the additional effect comes from the inhaler itself (approx. 1%), drug formulation, and other components (approx. 0.8%), as well as from manufacturing and distribution processes ($< 0.5\%$) [38]. This study was methodologically correct, as it covered all stages of the "life" of the inhalers tested (acquisition and initial processing of materials, production, distribution, use and disposal of the inhaler — LCA methodology). Similar data apply to other drugs with pMDI HFA 134a [40]. It is worth recalling that the HFA 227a propellant contained, for example, in the GKSw/LABA Flutiform™ 120 doses, demonstrates even higher GWP value — 295 g CO_2e per dose [41] *vs* Ventolin™ pMDI 134a 200 doses — approx. 120 g CO_2e per dose [42]. Also, the HFA 227a contained in pMDI Symbicort™ shows a very high GWP value [43]. Both, Flutiform™ pMDI and Symbicort™ pMDI, are not available on the Polish market.

The comparisons of pMDI HFA 134a with DPI for inhalers available on the Polish market are interesting. In a recently published study, Janson *et al.* [44] assessed the total annual carbon footprint of pMDI and DPI of Accuhaler (Diskus)™ and Ellipta™ types (Table 3).

The presented data show that the combination of fluticasone propionate with salmeterol in DPI results in a carbon footprint 32 times lower than in pMDI HFA 134a. On the other hand, preparations containing two or three medicinal substances in one inhaler resulted in a lower carbon footprint than using them in separate inhalers: by 12.6% for pMDI and by 23.2% for DPI [44]. Similar results are found in the publication by Wilkinson *et al.* [40].

Slightly different results were presented by Panigone et al., who were analyzing some inhalation drugs by Chiesi Farmaceutici S.p.A., also with the new HFA-152a propellant (drugs with this propellant are under study) (Table 4) [45]. It presents data on inhalers containing 120 doses and providing 200 μg beclometasone dipropionate/6 μg formoterol/nominal dose (Foster®) or 100 μg beclometasone/6 μg formoterol/12.5 μg glycopyrronium bromide per metered dose (Trimbow®).

The carbon footprint of the NEXThaler type DPI is approx. 15 times lower than the corresponding combination in case of pMDI HFA 134a.

Table 3. Comparison of GWP for frequently used pMDI and DPI (own modification according to [44])

Inhalers/drugs	GWP kg CO_2e/year
pMDI — Ventolin Evohaler®	205
pMDI — Seretide Evohaler®	234
Total	439
DPI — Seretide Accuhaler (Diskus)®	7.3
DPI — Relvar Ellipta®	9.5
Total	16.8

DPI — dry powder inhaler; GWP — global warming potential; pMDI — pressurized metered dose inhaler

On the other hand, the use of the new HFA 152a carrier in pMDI reduces the carbon footprint of the assessed preparations by approx. 8 times and it is only approx. 2 times higher than it is in case of NEXThaler. Recently, data on the Breezhaler® capsule type DPI was provided by Novartis AG for its combination drugs: indacaterol (IND)/mometasone furoate (MF) and IND/MF/glycopyrronium (IND/MF/GLY) [46]. These tests were performed in accordance with the recommended standards (GHG Protocol). The evaluation covered the entire life cycle of the product, including the device, active pharmaceutical ingredient (drugs) and optional sensor. The carbon footprint comparison was carried out for these products in 4 countries: France, Germany, the UK and Japan. Data from France are shown in Figure 3. For the first time, the authors reported the carbon footprint of the sensor, an optional electronic device (Propeller Health Sensor) facilitating the control of patient adherence to prescribed inhalation treatment, and registered by the European Medical Agency in 2020 for use with DPI Breezhaler [47].

They show that a Breezhaler containing IND/MF or ING/MF/GLY without a sensor "produces" approx. 0.4 kg CO_2e and approx. 0.38 kg CO_2e, respectively, per month of use. However, an inhaler with ING/MF/GLY with a sensor produces as much as about 0.5 kg of CO_2e per month.

Recently, Orion Pharma reported the carbon footprint of the Easyhaler® DPI, and the study was performed according to the LCA methodology (Table 5) [48 ,49].

Manufacturing process of the device, drug substance, lactose carrier, packaging and package leaflet for the patient turned out to be the most important source of emissions constituting approx. 60% of the total carbon footprint (CO_2e) of the product. By comparison, the distribution of the inhaler constitutes less than 2% of the total carbon footprint. Salbutamol Easyhaler® shows the highest carbon footprint associated with its production, as it requires more lactose than other medicines manufactured by this company.

Table 4. Carbon footprint of selected inhaled drugs by Chiesi Farmaceutici S.p.A. [45]

Inhalers/drugs	GWP g CO_2e/dose	GWP kg CO_2e/inhaler
pMDI — Foster® HFA 134a*	118.56	14.23
pMDI — Foster® HFA 152a*	14.50	1.74
pMDI — Trimbow® HFA 134a	118.99	14.28
pMDI — Trimbow® HFA 152a	14.34	1.61
DPI — Foster NEXThaler®	7.64	0,92

DPI — dry powder inhaler; GWP — global warming potential; pMDI — pressurized metered dose inhaler

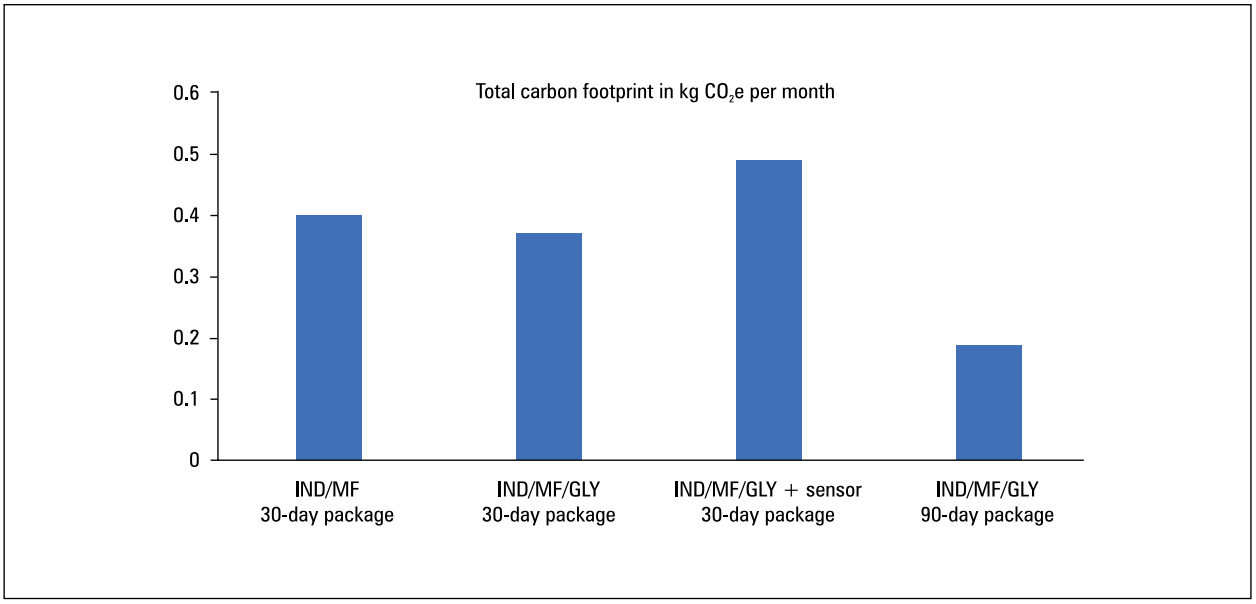

Figure 3. Carbon footprint in kg of CO_2e per month of medication use with DPI Breezhaler [46].
IND — indacaterol maleate; MF — mometasone furoate; GLY — glycopyrronium bromide

Not all pharmaceutical companies have disclosed the carbon footprint of their inhalers. For example, there are no data or only estimates for such popular DPIs as Turbuhaler® (AstraZeneca), Forspiro® (Sandoz AG) or Spiromax® (Teva Pharmaceuticals Industries Ltd.). There are also no data on inhalation chambers necessary for the use of pMDI in children and in some groups of adults.

Methods of reducing the negative environmental impact of inhalation drugs — a responsible view of inhalers in the context of the carbon footprint

Offered inhalers and the method of their use (until their disposal) will undoubtedly move towards reducing their carbon footprint, as this will be enforced by signed obligations and created law. Reducing the negative impact of inhalers on the environment can be achieved through a number of activities that involve inhaler and drug manufacturers, the payer, medical staff, and the patients themselves. Detailed actions should include the following [45, 50, 51]:

1. Implementation and strict adherence to an effective individual inhalation treatment plan (physician, patient);
2. Education and continuous verification of the correctness of the inhalation technique (health educator, physician, nurse, patient);
3. Reducing the use of SABA "on demand" in all types of inhalers by improving asthma and COPD control (physician, patient);
4. Optimal use of the inhalation chamber, usually associated with the improvement of the clinical efficacy of pMDI drugs (physician, patient);
5. Using inhalers for the last dose and not wasting doses by releasing the drug into the atmosphere (patient);
6. Introduction of pMDI with new propellants with lower GWP values, for example: HFA 152a (manufacturer, payer, physician);
7. Rational replacement of pMDI by DPI or MDLI (doctor);
8. Reducing the number of inhalers in a given patient through the wider use of drugs combined in one inhaler and the introduction of new two- or three-component formulations (manufacturer, physician, payer);
9. Creating DPI and MDLI inhalers with replaceable cartridges extending the time of using the inhaler (manufacturer);
10. Using DPI capsule for a larger number of doses, which requires actions that improve the inhalers (manufacturer);
11. Promoting the recycling of all inhalers (manufacturer, pharmacy, patient).

Replacing pMDI with DPI

Replacing pMDI with DPI is one of the ways to reduce the carbon footprint of inhalers, which was suggested a few years ago [52]. For example, it has been shown that reducing the number of pMDIs in favor of DPI in the UK from 70% to 13%

Table 5. Components of the carbon footprint level for various drugs in Easyhaler® DPI [49]

	Carbon footprint (g CO_2e) per inhaler		
Components influencing the carbon footprint	**Salbutamol**	**Fluticasone/Salmeterol**	**Budosonide/Formoterol**
Dose size in μg Number of doses	100 200	250/50 60	160/4.5 120
Raw materials for the production of inhaler components, packaging and patient information leaflets	142.3	142.3	142.3
Raw materials needed for drug and carrier production	0.74	1.9	0,50
Transportation of raw materials	11.5	11.50	11.40
Drug and carrier production	314.1	250.4	164.7
Assembling of the finished product	76.4	76.4	76.4
Product distribution	8.5	8.4	8.3
Utilization	72.4	72.4	72.4
Total	664.1	601.8	514.5

Table 6. Percent change in costs resulting from the replacement of various drug classes from pMDI to DPI — Poland compared to other European countries, data from European markets with the highest value (65 in-house modification).

	Poland [%]	Germany [%]	United Kingdom [%]	France [%]	Italy [%]	Spain [%]
SABA	290	147	290	171	277	304
SABA/SAMA	—*	205	—*	—*	—*	—*
ICS	80	81	121	101	107	99
LABA	90	92	92	100	99	107
ICS/LABA	93	91	95	97	100	92
ICS/LABA/LAMA	—*	155	148	142	161	183
Sum	96	102	107	107	106	104
Market value in mln $	271	1394	1293	894	685	751

*No equivalent in DPI.
DPI — dry powder inhaler; ICS — inhaled corticosteroid; LABA — long acting beta-2 agonist; LAMA — long acting anti-muscarinic agent; pMDI — pressurized metered dose inhaler; SABA — short acting beta-2 agonist; SAMA — short acting anti-muscarinic agent

will reduce CO_2 emissions by over 550 kt/year [53]. However, inhalers are not easily interchangeable and the selection of the correct device depends on many factors [54]. The best inhaler for a given patient should be chosen, following the principle of "the right inhaler for a given patient" and not "the same inhaler for all patients" [18, 51, 55, 56]. Each type of inhaler requires specific instructions for use and a new inhaler can be a problem for the patient, even if it would be better for some reason in the opinion of the doctor. Changing the inhaler may lead to a deterioration of the treatment effect [57, 58]. However, switching (both to a generic inhaler and to another one) in clinically justified cases in patients with asthma or COPD may reduce exacerbations and improve adherence as well as it can be a cheaper treatment [59]. It seems to be influenced by various local factors, therefore, data from one country (market) and a given type of inhaler cannot be uncritically transferred to other countries (markets) and inhalers [60]. As a general rule, if an obstructive bronchial disease is well controlled, the inhaler should not be changed without good reason. The change of each inhalation device should be agreed with the patient, who should be trained in the use of the new inhaler, and the use of the inhaler and inhalation technique should be controlled [54, 61, 62]. The limitation of the necessary inhaled drugs (regular and emergency) to one type of device (pMDI or DPI or MDLI or nebulizer), and in the case of DPI — to inhalers of the same generation is a significant facilitation for the patient [63, 64]. Switching drugs administered from pMDI to DPI may be associated with an increase in direct costs for most large EU countries, but not for Poland (Table 6) [65].

The highest cost of replacing pMDI with DPI will relate to SABA, also in Poland (growth by 290%). In the case of other drug classes in the country, lower costs of DPI vs. pMDI can be expected. There are substitutions in DPI for majority of pMDI drugs. Exception in the country includes ciclesonide, fenoterol, ipratropium bromide, fenoterol/ipratropium bromide and beclomethasone/formoterol/glycopyronium occurring only in pMDI.

Summary and conclusions

Precise determination of the carbon footprint for a given inhaler is not easy, so comparing different inhalers in this respect is a major challenge. In articular, the variety of DPI and nebulizer designs makes it difficult to perform simple comparisons of the carbon footprint between different device classes. There is not enough data on the carbon footprint of nebulizers to form a reliable opinion. So far, the assessment of the carbon footprint of pMDI inhalation chambers, nebulizer exhaled aerosol filters and many electronic devices (sensors) attached to or incorporated into the pMDI or DPI has been omitted. There are also no generally applicable uniform methods for assessing the carbon footprint of inhalers. The reduction of GHG related to the production and use of inhalers, despite a relatively low share of inhalation products in the total GHG emission, is part of the obligations that individual countries should undertake in order to implement the principles of international law. At the level of medical law, this obligation correlates with the need to exercise due diligence in the process of providing health services, including the selection of low-emission inhalers and providing patients with information on how to deal with inhalers.

Conclusions

1. The vast majority of inhalation drugs used in the treatment of asthma or COPD available in Poland are available in pMDI and DPI.
2. pMDI HFA 134a shows the highest carbon footprint, followed by MDLI and DPI. There is insufficient data on nebulizers to assess this group of inhalation devices.
3. The carbon footprint of DPI with a given drug is 13–32 times lower than it is in the corresponding pMDI.
4. It is necessary to disseminate new pMDI propellants with low greenhouse potential.
5. All types of inhalers should be available, as there are numerous groups of patients who cannot use DPI (children under 4–6 years of age, elderly COPD patients, severe forms of COPD/asthma with inspiratory flow < 30 L/min, in case of the drugs available only in pMDI).
6. We recommend caution and the use of current medical knowledge when replacing pMDI inhalers with DPI in patients with asthma or COPD. Changing the inhaler type solely on the basis of the dose equivalence is not appropriate.
7. There is an urgent need to implement a recycling system for all types of inhalers.

Conflict of interest

None declared.

References:

1. Peters GP. Carbon footprints and embodied carbon at multiple scales. Curr Opin Environ Sustain. 2010; 2(4): 245–250, doi: 10.1016/j.cosust.2010.05.004.
2. Houghton JT, Ding Y, Griggs DJ, Nouger M, van der Linden PJ, Dai X, Maskell K, Johnson CA. Climate change 2001: the scientific basis. Contribution of working group i to the third assessment report of the intergovernmental panel on climate change. Cambridge University Press, Cambridge/New York 2001.
3. EPA, 2020. https://www.epa.gov/ghgemissions/overview-greenhouse-gases#f-gases (26.10.2020).
4. Baron Ch. Is now the time to shake up the pMDI environment? Pulm Nasal Drug Deliv. 2020; 106: 10–13.
5. Our World in Data. http://ourlwordindata.org/co2-and-other-greenhouse-gas-emissions (20.08.2020).
6. Climate & Clean Air Coalition. Hydrofluorocarbons (HFC). https://www.ccacoalition.org/fr/slcps/hydrofluorocarbons-hfc (19.09.2020).
7. United Nations Environment Program, Montreal Protocol Secretariat, Ratification of the Kigali Amendment, information note (February 2017). http://conf.montreal-protocol.org/meeting/oewg/oewg-39/presession/briefingnotesfr/ratification_kigali_E.pdf (12.12.2020).
8. Bouley T, Boykoff M, Byass P et al. Climate-smart healthcare: low-carbon and resilience strategies for the health sector. Washington, DC: World Bank Group. 2017. http://documents.world bank.org/curated/en/322251495434571418/Climate-smart-healthcare-low-carbon-and-resilience-strategies-for-the-health-sector (22.09.2020).
9. Pichler PP, Jaccard IS, Weisz U, et al. International comparison of health care carbon footprints. Environl Res Lett. 2019; 14(6): 064004, doi: 10.1088/1748-9326/ab19e1.
10. Fletcher MJ, Upton J, Taylor-Fishwick J, et al. COPD uncovered: an international survey on the impact of chronic obstructive pulmonary disease [COPD] on a working age population. BMC Public Health. 2011; 11: 612, doi: 10.1186/1471-2458-11-612, indexed in Pubmed: 21806798.
11. Accessed United Nations Environment Programme. Report of the Medical Technical Options Committee (MTOC) 2018 Assessment Report. 2018. http://ozone.unep.org/Assessment_Panels/TEAP/Reports/MTOC/MTOC-AssessmentReport-2014.pdf (23.10.2020).
12. NICE encourages use of greener asthma inhalers. 08 April 2019. https://www.nice.org.uk/news/article/nice-encourages-use-of-greener-asthma-inhalers (13.12.2020).
13. Hodder R, Price D. Patient preferences for inhaler devices in chronic obstructive pulmonary disease: experience with Respimat Soft Mist inhaler. Int J Chron Obstruct Pulmon Dis. 2009; 4: 381–390, doi: 10.2147/copd.s3391, indexed in Pubmed: 19888356.

14. GINA Report 2020. Global Strategy for Asthma Management and Prevention. 2020 GINA MAIN REPORT. https://ginasthma.org/gina-reports/ (10.10.2020).
15. GOLD 2020 report — Global Initiative for Chronic Obstructive Lung Disease. https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf (10.10.2020).
16. Emeryk A, Pirożyński M, Mazurek H. Polski Przewodnik Inhalacyjny. Via-Medica, Gdańsk 2021.
17. Lavorini F, Corrigan CJ, Barnes PJ, et al. Aerosol Drug Management Improvement Team. Retail sales of inhalation devices in European countries: so much for a global policy. Respir Med. 2011; 105(7): 1099–1103, doi: 10.1016/j.rmed.2011.03.012, indexed in Pubmed: 21489771.
18. Laube BL, Janssens HM, de Jongh FHC, et al. European Respiratory Society, International Society for Aerosols in Medicine. What the pulmonary specialist should know about the new inhalation therapies. Eur Respir J. 2011; 37(6): 1308–1331, doi: 10.1183/09031936.00166410, indexed in Pubmed: 21310878.
19. Emeryk A, Pirożyński M, Emeryk-Maksymiuk J. Dry powder inhalers — between the doctor and the patient. Adv Respir Med. 2018; 86(1): 44–52, doi: 10.5603/ARM.2017.0061, indexed in Pubmed: 29490421.
20. Ramowa Konwencja Narodów Zjednoczonych w sprawie zmian klimatu, z dnia 9 maja 1992 r., Dz.U. 1997 r., nr 45, poz. 286.
21. Protokół z Kioto do Ramowej Konwencji Narodów Zjednoczonych w sprawie zmian klimatu z dnia 11.12.1997 r., Dz.U. 2005 r., nr 203, poz. 1684.
22. Matsuo T. Climate change research project, discussion papers, for the design of effective framework of Kyoto mechanisms. Kanagawa, 1999.
23. Porozumienie paryskie do Ramowej konwencji Narodów Zjednoczonych w sprawie zmian klimatu z dnia 12 grudnia 2015 r., Dz.U. 2017 r., poz. 36.
24. Rozporządzenie Parlamentu Europejskiego i Rady (WE) nr 1005/2009 z dnia 16 września 2009 r. w sprawie substancji zubożających warstwę ozonową (Tekst mający znaczenie dla EOG).
25. Rozporządzenie Parlamentu Europejskiego i Rady (WE) nr 517/2014 z dnia 16 kwietnia 2014 r., w sprawie fluorowanych gazów cieplarnianych i uchylenia rozporządzenia (WE) nr 842/2006 (Tekst mający znaczenie dla EOG).
26. Ustawa z dnia 15 maja 2015 roku o substancjach zubożających warstwę ozonową oraz o niektórych fluorowanych gazach cieplarnianych, Dz.U. 2015 r., poz. 881.
27. Protokół montrealski w sprawie substancji zubożających warstwę ozonową — międzynarodowe porozumienie dotyczące przeciwdziałania dziurze ozonowej z dnia 16 września 1987, Dz.U. 1992 r., nr 98, poz. 490.
28. Poprawka z Kigali z dnia 15 października 2016 r., nr 2017/1541, Decyzja Rady UE sprawie zawarcia, w imieniu Unii Europejskiej, poprawki z Kigali do Protokołu montrealskiego w sprawie substancji zubożających warstwę ozonową.
29. Konstytucja RP z dnia 2 kwietnia 1997 r., Dz.U. 1997 r., nr 78, poz. 483.
30. Ustawa z dnia 9 listopada 2018 roku o ratyfikacji Poprawek do Protokołu montrealskiego w sprawie substancji zubożających warstwę ozonową, sporządzonego w Montrealu dnia 16 września 1987 r., przyjętych w Kigali dnia 15 października 2016 r., Dz.U. 2018 r., poz. 2254.
31. Sekretariat Konwencji – art. 1 pkt 3 Protokołu Montrealskiego. https://ozone.unep.org/ozone-secretariat-launches-new-website (27.12.2020).
32. Ustawa o zawodach lekarza i lekarza dentysty z dnia 05 grudnia 1996 r., tj. Dz.U. 2020 r., poz. 514, ze zm.
33. British Thoracic Society, Position Statement the environment and lung health 2020. www.brit-thoracic.org.uk%2Fdocument-library%2Fgovernance-and-policy-documents%2Fposition-statements%2Fenvironment-and-lung-health-position-statement-2020%2F&usg=AOvVaw0V6ybLM-eOx2ZvUv-4VYtf9 (27.12.2020).
34. Ustawa o utrzymaniu czystości i porządku w gminach z dnia 13 września 1996 r., Dz.U. 2020 r., poz. 1439.
35. Jeswani H, Azapagic A. Life cycle environmental impacts of inhalers. Journal of Cleaner Production. 2019; 237: 117733, doi: 10.1016/j.jclepro.2019.117733.
36. Goulet B, Olson L, Mayer B. A comparative life cycle assessment between a metered dose inhaler and electric nebulizer. Sustainability. 2017; 9(10): 1725, doi: 10.3390/su9101725.
37. Kleinekorte J, Fleitmann L, Bachmann M, et al. Life cycle assessment for the design of chemical processes, products, and supply chains. Annu Rev Chem Biomol Eng. 2020; 11: 203–233, doi: 10.1146/annurev-chembioeng-011520-075844, indexed in Pubmed: 32216728.
38. Hänsel M, Bambach T, Wachtel H. Reduced environmental impact of the reusable Respimat Soft Mist™ inhaler compared with pressurised metered-dose inhalers. Adv Ther. 2019; 36(9): 2487–2492, doi: 10.1007/s12325-019-01028-y, indexed in Pubmed: 31317391.
39. Ortsäter G, Borgström F, Soulard S, et al. A budget impact model to estimate the environmental impact of adopting RESPIMAT re-usable in the Nordics and Benelux. Adv Ther. 2019; 36(12): 3435–3445, doi: 10.1007/s12325-019-01114-1, indexed in Pubmed: 31625130.
40. Wilkinson AJK, Braggins R, Steinbach I, et al. Costs of switching to low global warming potential inhalers. An economic and carbon footprint analysis of NHS prescription data in England. BMJ Open. 2019; 9(10): e028763, doi: 10.1136/bmjopen-2018-028763, indexed in Pubmed: 31662306.
41. Mueller-Walz R, Fueg LM. Medicinal aerosol formulations, 2014. https://www.google.com/patents/US20140314684 (15.03.2021).
42. Atherton M. Environmental impact of inhalers, 2017. https://www. Great -ermanchester-ca.gov.uk/download/meetings/id/2423/environmental_ impact_ of_ inhalers (27.09.2020).
43. Some Specific Inhalers – Ventolin™, Flutiform™, Symbicort™ MDI. https://greeninhaler.org/some-specific-inhalers-ventolin-flutiform-symbicort-mdi/ (25.10.2020).
44. Janson C, Henderson R, Löfdahl M, et al. Carbon footprint impact of the choice of inhalers for asthma and COPD. Thorax. 2020; 75(1): 82–84, doi: 10.1136/thoraxjnl-2019-213744, indexed in Pubmed: 31699805.
45. Panigone S, Sandri F, Ferri R, et al. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. BMJ Open Respir Res. 2020; 7(1): e000571, doi: 10.1136/bmjresp-2020-000571, indexed in Pubmed: 32238349.
46. Case study*: Breezhaler® Carbon Footprint. https://www.novartis.com/our-company/corporate-responsibility/environmental-sustainability/climate/case-study-breezhaler-carbon-footprint (12.12.2020).
47. https://www.google.pl/search?sxsrf=ALeKk03kxPk3x1748Ld-79QI__e7wATmvEQ:1594103429530&source=univ&tbm=isch&q=breezhaler+sensor&sa=X&ved=2ahUKEwigzJuFwrrqAhVJlosKHbNrDQMQsAR6BAgIEAE&biw=1536&bih=754#imgrc=8MZSL3GA-AsqYM (10.10.2020).
48. Product Carbon Footprint: Life Cycle Assessment Report for Orion Corporation, Orion Pharma. A study of 4 varieties of Easyhalers. Carbon Footprint Ltd 2020.
49. Carbon Footprint Assessment of Orion's Dry Powder Inhalers. https://www.orion.fi/en/Sustainability/stories-about-responsibility/inhaler-environmental-footprint/ (25.10.2020).
50. Keeley D, Scullion JE, Usmani OS. Minimising the environmental impact of inhaled therapies: problems with policy on low carbon inhalers. Eur Respir J. 2020; 55(2): 2000048, doi: 10.1183/13993003.00048-2020, indexed in Pubmed: 32108081.
51. Usmani O, Scullion J, Keeley D. Our planet or our patients — is the sky the limit for inhaler choice? The Lancet Respiratory Medicine. 2019; 7(1): 11–13, doi: 10.1016/s2213-2600(18)30497-1, indexed in Pubmed: 30553845.
52. Hillman T, Mortimer F, Hopkinson NS. Inhaled drugs and global warming: time to shift to dry powder inhalers. BMJ. 2013; 346: f3359, doi: 10.1136/bmj.f3359, indexed in Pubmed: 23714412.
53. Wynes S, Nicholas K. The climate mitigation gap: education and government recommendations miss the most effective individual actions. Environmental Research Letters. 2017; 12(7): 074024, doi: 10.1088/1748-9326/aa7541.
54. Lavorini F, Braido F, Baiardini I, et al. SIAAC-SIMER. Asthma and COPD: Interchangeable use of inhalers. A document of Italian Society of Allergy, Asthma and Clinical Immmunology

(SIAAIC) & Italian Society of Respiratory Medicine (SIMeR). Pulm Pharmacol Ther. 2015; 34: 25–30, doi: 10.1016/j.pupt.2015.07.005, indexed in Pubmed: 26209820.
55. Mahler DA. The role of inspiratory flow in selection and use of inhaled therapy for patients with chronic obstructive pulmonary disease. Respir Med. 2020; 161: 105857, doi: 10.1016/j.rmed.2019.105857, indexed in Pubmed: 32056720.
56. Pedersen S, Dubus JC, Crompton GK, et al. ADMIT Working Group. The ADMIT series — issues in inhalation therapy. 5) Inhaler selection in children with asthma. Prim Care Respir J. 2010; 19(3): 209–216, doi: 10.4104/pcrj.2010.00043, indexed in Pubmed: 20640390.
57. Roggeri A, Micheletto C, Roggeri DP. Inhalation errors due to device switch in patients with chronic obstructive pulmonary disease and asthma: critical health and economic issues. Int J Chron Obstruct Pulmon Dis. 2016; 11: 597–602, doi: 10.2147/COPD.S103335, indexed in Pubmed: 27051283.
58. Thomas M, Price D, Chrystyn H, et al. Inhaled corticosteroids for asthma: impact of practice level device switching on asthma control. BMC Pulm Med. 2009; 9: 1, doi: 10.1186/1471-2466-9-1, indexed in Pubmed: 19121204.
59. Bloom CI, Douglas I, Olney J, et al. Cost saving of switching to equivalent inhalers and its effect on health outcomes. Thorax. 2019; 74(11): 1078–1086, doi: 10.1136/thoraxjnl-2018-212957, indexed in Pubmed: 31383774.
60. Rhee CK, van Boven JFM, Yau Ming SW, et al. Does changing inhaler device impact real-life asthma outcomes? Clinical and economic evaluation. J Allergy Clin Immunol Pract. 2019; 7(3): 934–942, doi: 10.1016/j.jaip.2018.09.027, indexed in Pubmed: 30292924.
61. Bjermer L. The importance of continuity in inhaler device choice for asthma and chronic obstructive pulmonary disease. Respiration. 2014; 88(4): 346–352, doi: 10.1159/000363771, indexed in Pubmed: 25195762.
62. Levy ML, Dekhuijzen P, Barnes PJ, et al. Inhaler technique: facts and fantasies. A view from the Aerosol Drug Management Improvement Team (ADMIT). NPJ Prim Care Respir Med. 2016; 26: 16017, doi: 10.1038/npjpcrm.2016.17, indexed in Pubmed: 27098045.
63. Price D, Bosnic-Anticevich S, Briggs A, et al. Inhaler Error Steering Committee. Inhaler competence in asthma: common errors, barriers to use and recommended solutions. Respir Med. 2013; 107(1): 37–46, doi: 10.1016/j.rmed.2012.09.017, indexed in Pubmed: 23098685.
64. Usmani OS. Choosing the right inhaler for your asthma or COPD patient. Ther Clin Risk Manag. 2019; 15: 461–472, doi: 10.2147/TCRM.S160365, indexed in Pubmed: 30936708.
65. Pritchard JN. The climate is changing for metered-dose inhalers and action is needed. Drug Des Devel Ther. 2020; 14: 3043–3055, doi: 10.2147/DDDT.S262141, indexed in Pubmed: 32801643.