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Evaluation and Mitigation of Carbon Footprint of Medical Inhalers

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Pressurized metered dose inhalers (pMDIs) contain propellants with high Global Warming Potential. This paper compares six pMDI products from the Polish market in terms of their contribution to environmental burden by analyzing the release and residuals of greenhouse gases during use and disposal. The results show that these similar medical products have markedly different carbon footprint values (12-22.5 kg CO_2e), which might be mitigated by certain measures involving technical and legal actions.

1. Introduction

The Kigali Amendment (2016) to Montreal Protocol defined new conditions on the use of certain liquid organic propellants (LOPs) in, so called, pressurized metered dose inhalers (pMDIs) which are commonly used aerosol drug delivery devices for the treatment of asthma and other inflammatory lung diseases (Pritchard, 2020; Emeryk et al., 2021). Although the amount of LOPs in single can is low, typically in the range of 10-20 g (Wyleziński, 2022), the total release of LOPs from pMDIs into the atmosphere leads to a measurable environmental burden. This is due to high values of the Global Warming Potential (GWP) value of LOPs and a massive number of pMDIs consumed (over 800 million cans worldwide sold per year, Emeryk, 2021). The contribution of pMDIs among other inhalers varies from country to country, ranging from 35% (Japan) to nearly 90% (USA), (Pritchard, 2020). In Poland, pMDIs account for 45% of all inhalers sold, Figure 1.
The GWP value of the hydrofluoroalkane HFA134a (1,1,1,2-tetrafluoroethane), which is currently the most widely used LOP in pMDI equals to 1300 kg CO_2e. It might be noted though that novel propellants with lower GWP values are under development (Pritchard, 2020), although they must be thoroughly tested for safety for use as an ingredient in medical products. A detailed discussion on the actual carbon footprint (CF) of pMDIs cannot be carried out without knowing specific figures for LOPs emission from such inhalers. This paper is focused on determining and comparing the propellant content and emission of six pMDIs commonly prescribed in Poland. These data are next used to calculate and compare the CFs of the inhalers.

2. Materials and Methods

LOP emissions from six pMDI products, labeled A-F (Table 1, Fig. 2) was tested over the lifetime of the inhalers using a gravimetric method. Each inhaler was weighed using AS 220/C/2 balance (Radwag, Poland) after releasing a series of 10 successive doses of the drug. The data were then converted to the mass released in a single dose and averaged. The content (and GWP) of the active pharmaceutical ingredients (API) contained in the products was neglected due to their low content compared to the LOP (up to 0.25 mg vs. above 50 mg of the propellent per dose, i.e., below 0.5% w/w). The estimations of CF were done using LCA analysis using openLCA® software (https://www.openlca.org/).

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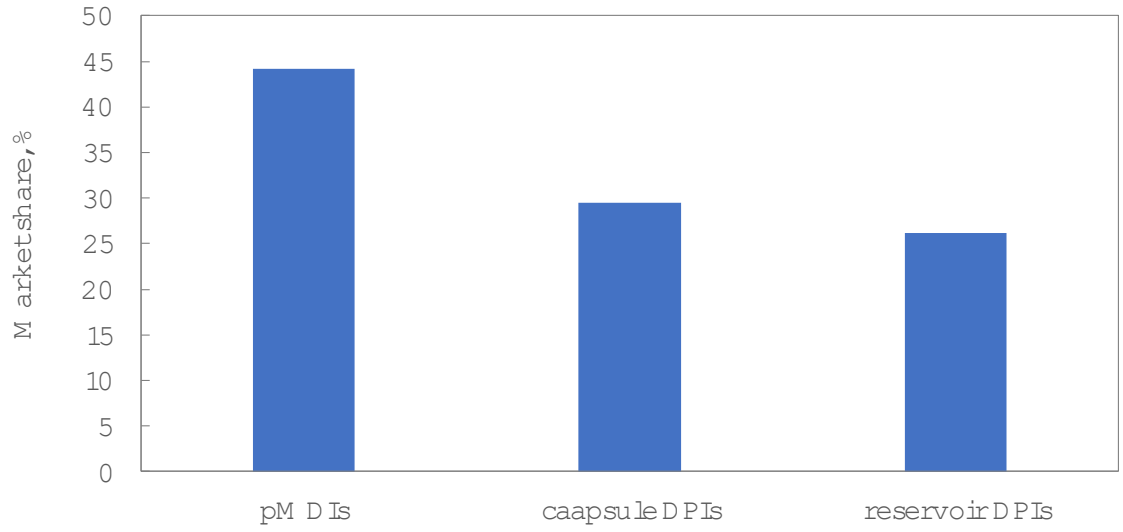

Figure 1. Market share of personal dosing inhalers in Poland (2019-2020). pMDIs – pressurized metered dose inhalers, DPIs – dry powder inhalers. Data based on Emeryk et al. (2021).

Table 1: Pressurized metered dose inhalers (pMDIs) studied. All contain HFA134a as a propellant.

Product code	API and dose per puff	Number of doses per can (declared)
A	Ciclesonide (160 μg)	120
B	Fenoterol (50 μg) + ipratropium bromide (21 μg)	200
C	Fenoterol (100 μg)	200
D	Fluticasone (250 μg)	120
E	Salmeterol (25 μg) + fluticasone (250 μg)	120
F	Salbutamol (100 μg)	200

API – active pharmaceutical ingredient

A B C D E F

Figure 2. pMDI inhalers studied in this work

3. Results and Discussion

Table 2 shows the initial and the final weights of the inhalers after releasing the declared number of doses. The average LOP masses released per single dose shown in Figure 3 indicate that there are differences between the inhalers tested. Some pMDIs are much more environmentally friendly (e.g., B and C, with the LOP emission

of approximately 50 mg/dose) that others (e.g., D, E and F - about 75 mg/dose). After calculating the carbon footprint for HFA134a as the propellant (GWP = 1300 kg CO_2e), values in the range of 65-97.5 g CO_2e per single drug emitted dose were obtained, which is equivalent to 9.36-19,5 kg CO_2e for all doses declared for a given inhaler. It can be seen (Table 2) that all inhalers allowed the release of more doses than declared by the manufacturer, but a tail-off effect was observed for doses above the nominal dose number (Figure 4). This means that pMDIs still contain LOP (up to about 3 g) after releasing the declared number of doses.

Table 2: Pressurized metered dose inhalers (pMDIs) studied

Product code	Initial mass [g]	Mass after releasing the declared number of drug doses [g]	Final mass after releasing all available drug doses [g]
A	25.229	18.152	16.255
B	34.305	24.115	21.207
C	34.033	24.037	21.251
D	26.779	17.833	14.415
E	31.259	22.682	20.491
F	37.728	22.681	20.714

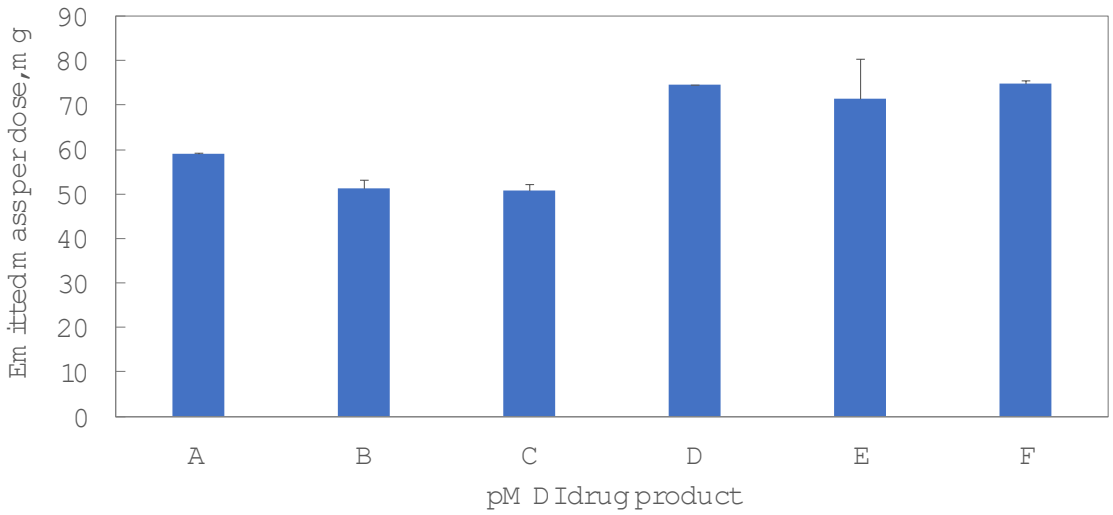

Figure 3. Emitted mass of LOP (HFA134a) per drug dose. Error bars denote standard deviation.

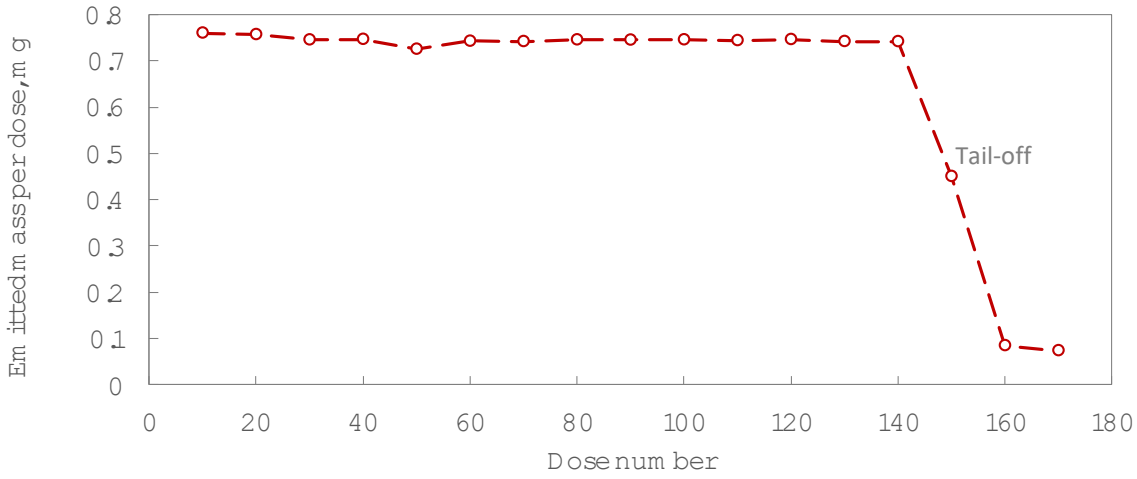

Figure 4. Example of the relationship of emitted LOP mass per drug dose vs the dose number (product D).

On the other hand, there is no direct correlation between the initial can contents, i.e., the number of nominal drug doses in a given medical product, and the mass of the “residual” propellant remaining after their release (Figure 5). This suggests that if the can after using the drug is not properly recycled, the residual propellant will form a waste with a measurable environmental burden.

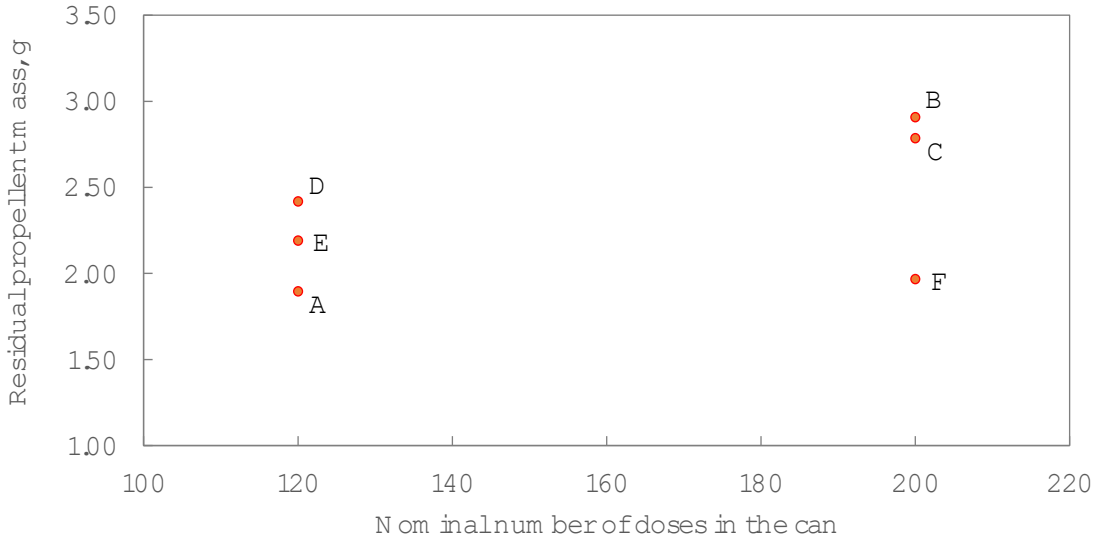

Figure 5. The mass of residual LOP in the pMDIs (A-F) after the release of the nominal number of doses.

The emissions data can be used to further calculate the CF of pMDIs using LCA methodology, which also allows comparison of pMDI with other types of inhalers (Goulet et al. 2017). This can help to decide whether more environmentally friendly propellants should be developed, or whether pMDIs should be replaced by inhalers with a different operating principle (nebulizers, dry powder inhalers - DPIs, soft mist inhalers – SMI, and others) that allow the same drug doses to be delivered, but with a lower environmental impact expressed by CF.

Estimates according to openLCA® methodology, which took into account the contents of the can, the aluminium can itself and the plastic actuator, showed that LOP emissions from the tested pMDIs account for 96-98% of the total CF of these medical products. These results, confirming the high contribution of LOP emissions, are consistent with published results obtained for the use and end-of-life phases of cradle-to-grave life cycle analysis for pMDI, as opposed to DPI, where most of the contribution to CF comes from the materials of the inhaler (Panigone et al., 2020).

However, also including the residual amount of the propellant remaining in the can, the carbon footprint values for the pMDIs (Figure 6) differ from those predicted based on LOP emissions during inhaler use, which were shown in Figure 3. The lowest CF was found for inhaler A (12 kg CO_2e; nominal content: 120 doses), and the highest for inhaler F (22.5 kg CO_2e; nominal content 200 doses). A large difference between 120-dose and 200-dose inhaler is evident here, although this is not a rule, and the differences can be smaller (B, C, and F contain 200 doses, A, D and E contain 120 doses). This is due to the fact that amounts of remaining propellant in the containers are not equal.

The results show that there is room for improvement for reduction of CF of pressurised inhalers, for instance, by developing new propellants for drugs delivered with pMDIs. Works on pMDIs that use new propellants, for instance HFA-152a (1,1-difluoroethane) with much lower GWP = 120 kg CO_2e, are in progress (Jeswani and Azapagic, 2019; Panigone et al., 2020), however the process of propellant replacement is complex and will be expensive. This is dictated by the need to ensure good stability in the formulations of various drugs, but also the safety of inhaling the new propellant. Another way to reduce the drug footprint of pMDIs is to use formulations with two or three drugs in a single pMDI, meaning that through a single propellant release, a patient can get doses of two or three APIs at the same time.

The carbon footprint of pMDIs can also be mitigated by replacing them with other types of inhalers characterized by lower CF. Indeed, DPIs or nebulizers have been shown to have significantly lower CF (Janson et al., 2020; Goulet et al., 2017). However, such swap of drug delivery device is not always possible and may not be acceptable if it can be associated with worsening treatment outcomes (Pritchard, 2020). The economic cost of such a change may also be unacceptable to patients.

The most obvious strategy that can be proposed to reduce CF of pMDIs is to set up the recycling system for used cans (with a residual propellant) and plastic actuators, which will protect the environment from contamination by residual LOP contained in inhalers after their prescribed use (Keelay et al., 2020). In some countries (e.g,, in the UK), some actions have been already undertaken (Recycling Magazine, 2023). It can be proposed that a modern and secure recycling system in the future can take advantage of cutting-edge data processing concepts such as blockchain technology (Sosnowski and Sepczuk, 2023).

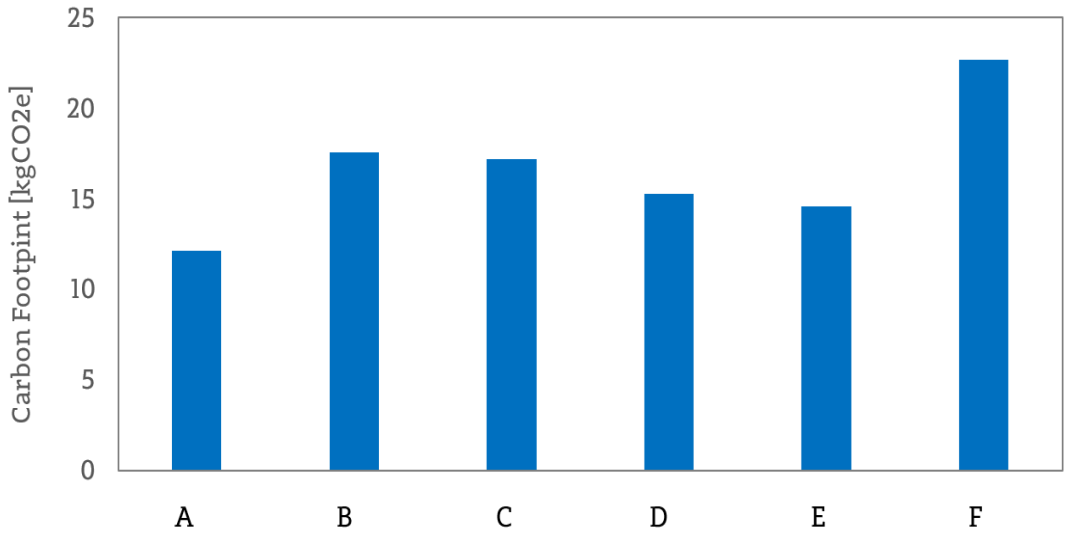

Figure 6. The total Carbon Footprint of studied inhalers (pMDIs: A-F) estimated by LCA approach.

4. Conclusions

Quantitative analysis of carbon footprint of six pressurised metered dose inhalers (pMDIs) of pulmonary drugs commonly used in Poland showed that they differ in LOP content and emissions (50 - 75 mg of HFA emitted per dose). There is also a difference in the residual propellant dose in the pressurized container after all claimed drug doses have been released (1.9 - 2.9 g of HFA per container). Converting these figures to the carbon footprint of inhalers leads to GWP values equal to 9.4-19.5 kg CO_2e for all released nominal doses and 12-22.5 kg CO_2e for the entire LOP contained in the product (i.e., including its residual content). This contributes to the environmental burden, given the widespread use of such inhalers.
Mitigation of this burden should be done by replacing pMDIs with other types of inhalers (nebulizers, dry powder inhalers) whenever possible, but also by recycling used cans which usually contain the residual HFA gases. The development of multi-drug pMDIs or drug formulations containing new propellants with lower GWP values is also possible, but it requires significant technical effort and thorough research into the safety of new LOPs and formulations for the inhalation treatment of respiratory diseases.

Nomenclature

DPI – dry powder inhaler
LCA – life cycle assessment
LOP - liquid organic propellant
HFA – hydrofluoroalkane
HFA134a - 1,1,1,2-tetrafluoroethane
HFA152a - 1,1-difluoroethane
GWP – Global Warming Potential, kg CO_2e
CF – Carbon Footpring, kg CO_2e
pMDI – pressurized metered dose inhaler

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