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Life cycle environmental impacts of inhalers

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ABSTRACT

Pressurised metered-dose inhalers are a method of choice for delivering drugs into lungs for the treatment of asthma and chronic obstructive pulmonary disease across the globe. HFC-134a and HFC-227ea propellants, which are currently used in these inhalers, have significant global warming potentials. To reduce the climate change impact of inhalers, several options are available to the industry, including alternative devices, such as dry powder inhalers and nebulisers. In addition, the manufacturers can reduce the propellant quantity per dose or use a different propellant with a lower global warming potential, such as HFC-152a. This study evaluates the life cycle environmental impacts of different types of inhaler and investigates possible scenarios to reduce their impacts. The environmental impacts are estimated through life cycle assessment, following the ReCiPe impact assessment method. The results suggest that HFC-152a inhaler has the lowest impacts for ten out of 14 categories considered, while the dry powder inhaler is the worst option for eight impacts; however, it has the lowest climate change and ozone depletion impacts. Considering the annual use of pressurised metered-dose and dry powder inhalers in the UK, they generate 1.34 Mt CO_2 eq., largely due to HFC-134a inhalers. This represents 4.3% of greenhouse gas emissions of the NHS (National Health Service). Replacing HFC-134a with HFC-152a would reduce the climate change and ozone depletion impacts of inhalers in the UK by 90%–92%. Most other environmental impacts would also decrease significantly (28%–82%). Switching from pressurised metered-dose inhalers to dry powder inhalers would lead to an even higher reduction in the climate change impact (96%). However, several other impacts would increase significantly, including human toxicity, marine eutrophication and fossil depletion. Since changing propellants or replacing pressurised metered-dose inhalers with dry powder inhalers requires further research and development, pharmaceutical companies should continue to work on minimising propellant usage in inhalers and on achieving higher rates of recycling of current inhalers.

1. Introduction

The healthcare sector is a significant contributor to greenhouse gas (GHG) emissions globally. It accounts for 10% of national GHG emissions in the USA (Eckelman and Sherman, 2016), 7% in Australia (Malik et al., 2018) and 4.6% in Canada (Eckelman et al., 2018). In 2015, the sector in England emitted 26.6 Mt of GHG emissions (Sustainable Development Unit, 2016), contributing 7% to England's annual emissions of 370 Mt CO_2 eq. (NAEI, 2018). Currently, 57% of GHG emissions (15.2 Mt CO_2 eq.) from healthcare in England are related to procurement (Sustainable Development Unit, 2016). Of this, 24% (3.6 Mt CO_2 eq.) is from pharmaceuticals. Pressurised metered-dose inhalers (pMDIs) are the largest single contributors to the pharmaceutical-related GHG emissions (Sustainable Development Unit, 2016).

Pressurised metered-dose inhalers were first introduced in 1956 by Riker Laboratories for the treatment of asthma and chronic obstructive pulmonary disease (COPD) (Stein and Thiel, 2017). Since then, pMDIs have played a vital role in the delivery of a number of medications through the inhalation route and continue to be the major method of choice for the delivery of drugs for the management of asthma and COPD across the globe. pMDIs rely on the driving force of propellants, which comprise the bulk of any pMDI formulation, to atomise droplets containing drug and excipients for deposition in the lungs (Ferguson et al., 2018). It is estimated that more than 630 million pMDIs are manufactured each year globally, using around 10,000 tonnes of propellants (UNEP, 2014).

Originally chlorofluorocarbons (CFC), such as ozone-depleting

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CFC-11, CFC-12 and CFC-114, were used as propellants in pMDIs (Myrdal et al., 2014). With the ratification of the Montreal Protocol on Substances that Deplete the Ozone Layer in 1989, which banned the use of CFCs (UNEP, 1987), an industry-wide transition to hydrofluorocarbon (HFC, also known as hydrofluoroalkane or HFA) propellants, such as HFC-134a and HFC-227ea, ensued globally. In addition to the ozone-related benefits, the move to HFCs from CFCs resulted in an order of magnitude reduction in the global warming potential (GWP) associated with propellant use (see Table S1 in the Supplementary Information). Despite that, the GWPs of HFC-134a and HFC-227ea propellants are still regarded by many as high and the healthcare industry is exploring various options for further reducing the GHG emissions associated with pMDIs. Some of these options include:

- the use of alternative devices, such as dry powder inhalers (DPI) and nebulisers;
- reducing the amount of propellant used per dose; and
- using different propellants with a lower GWP in pMDIs.

DPIs and nebulisers are already in widespread use for certain drugs but it is not yet technically or economically feasible to replace pMDIs completely due to cost, technical and patient-acceptability reasons (UNEP, 2016). Techniques for reducing the amount of propellant and hence its emission into the atmosphere include reducing the size of metering valves and recovery of propellant from spent or part-consumed pMDIs. Regarding the use of different propellants, HFC-152a (1,1,-difluoroethane) has been suggested as a potential replacement for current pMDI propellants and is currently being investigated by the manufacturer for its safety and formulation behaviour (Noakes and Corr, 2016).

Production of pharmaceutical products is a complex and resource−intensive process, which can have significant impacts on the environment (Parvatker et al., 2019). Pharmaceutical companies across the globe are adopting different sustainability-related practices in an attempt to minimise their impacts (Chaturvedi et al., 2017). These practices include use of green chemistry principles for the reduction or replacement of hazardous substances (Cue and Zhang, 2009), adoption of energy-efficiency measures in manufacturing (Müller et al., 2014) and application of the eco-design concept in product development (Baron, 2012). Moreover, some companies are using life cycle assessment (LCA) to identify, evaluate and implement such measures (De Soete et al., 2017; Jiménez-González et al., 2011). However, often such assessments apply fast screening or streamlined methods for hotspot determination (Cespi et al., 2015; De Soete et al., 2017) rather than full LCA studies. Moreover, these assessments are often not available in the public domain. The lack of primary data provided by the pharmaceutical industry to construct life cycle inventories is also one of the most important reason for the lack of LCA studies on pharmaceutical products (De Soete et al., 2017). To address these data gaps, some studies (Parvatker et al., 2019; Ponder and Overcash, 2010) have focussed on developing life cycle inventories for active pharmaceutical ingredients (APIs). Others have assessed the LCA impacts of APIs (Brunet et al., 2014; McAlister et al., 2016; Wernet et al., 2010). Parvatker et al. (2019) also estimated cradle-to-gate GHG emissions of 20 anaesthetic drugs and found that GHG emissions of drugs varied enormously, from 11 kg to 3000 kg CO_2 eq. per kg of APIs, depending on the number of synthesis steps needed in the manufacturing of the drug. Since the use of organic solvents is the main hotspot in the synthesis of APIs, LCA studies have also evaluated cleaner production options with the aim of or reducing their use or replacing them (Amado Alviz and Alvarez, 2017; Leone et al., 2018).

In line with the other pharmaceutical products, there is also limited information on the environmental impacts of inhalers. Goulet et al. (2017) compared carbon footprints of a HFC-134a inhaler with a nebuliser and found that in comparison to a nebuliser, pMDI has a 2−3 times higher GWP. A study by GlaxoSmithKline (2014) found that the GWP of their HFC-134a inhalers was 17 times higher than that of DPI, while UNEP (2014) report provided GWP estimates for HFC-134a, HFC-227ea and DPIs. Unlike the previous studies which focused on GWP only, this study aims to evaluate a range of life cycle environmental impacts of pMDIs and DPIs. For pMDIs, three different propellants are considered: HFC-134a, HFC-227ea and HFC-152a. As far as the authors are aware, this is the first study to quantify the life cycle impacts of inhalers using a comprehensive set of environmental impact indicators, accompanied with sensitivity and uncertainty analyses. The impacts are estimated both for the individual inhalers and for their annual use, with the latter focused on UK situation. Possible options to reduce the environmental impacts of inhalers are also considered. It is hoped that the results of this research will be useful for the healthcare industry and policy makers.

The next section provides details on the different types of inhaler considered and gives an overview of the methodology used to assess the environmental impacts. The results are presented in Section 3, followed by the conclusions and recommendations in Section 4.

2. Methodology

The environmental impacts have been estimated through LCA, following the ISO 14040/14044 guidelines (ISO, 2006a, b). The next sections detail the goal, scope, inventory data and the impact assessment methodology used in the study.

2.1. Goal and scope of the study

The aim of this study is to estimate the environmental impacts of inhaler devices used for the delivery of inhalation medicines and evaluate possible options for reducing their impacts. Two types of inhaler are considered: pMDI and DPI. Their typical designs are illustrated in Fig. 1. For pMDIs, the impacts of three types of propellant are investigated: HFC-134a, HFC-227ea and HFC-152a. The first two are currently used in pMDIs, while HFC-152a is seen by the pharmaceutical industry as a candidate to replace the existing propellants to reduce the climate change impact of inhalers.

The scope of the study is from 'cradle to grave' including production of the device and the propellants (for pMDIs), as well as the use and end-of-life disposal of inhalers (Fig. 2). The production of APIs is not considered and it is independent of the delivery platform (inhaler type) used. The analysis is first carried out for individual inhalers, with the functional unit defined as 'delivery of 1 dose of inhaled medicine'. The results are then scaled up to consider the impacts based on the annual usage of inhalers in the UK. For the latter, various alternative scenarios for reducing the impacts are also explored.

2.2. Inventory data

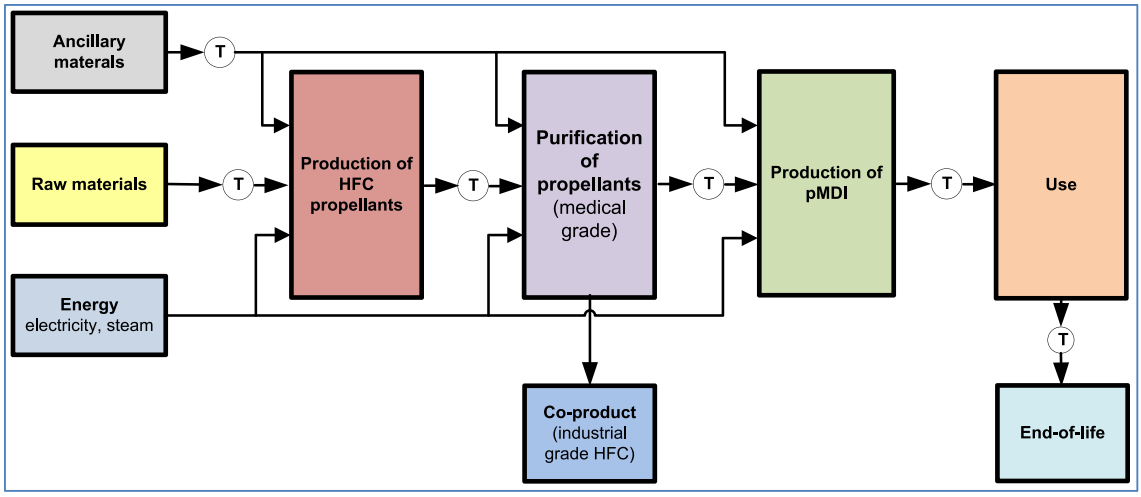
Most of the primary data for inhalers and propellants have been obtained directly from industry, supplemented by literature where necessary. The background data are from Ecoinvent V3.3 database (Ecoinvent, 2016). This is detailed in the following sections.

2.2.1. Pressurised metered-dose inhaler

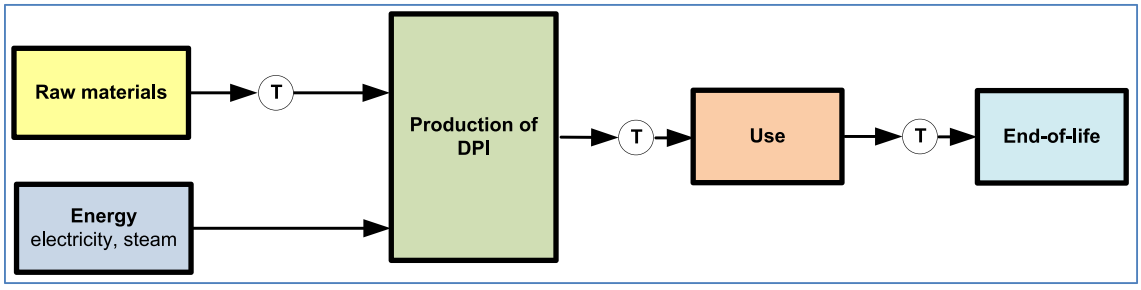
The pMDI device consists of three components: an inhaler device, a propellant and a drug. As mentioned earlier, the drug is not considered. For effective delivery of some drugs, co-solvents, such

a) Pressurised metered-dose inhaler (pMDI) b) Dry powder inhaler (blister-based Diskus)

Fig. 1. Typical design of pressurised metered-dose and dry powder inhalers.



a) Pressurised metered-dose inhaler (pMDI)



b) Dry powder inhaler (DPI)

Fig. 2. Life cycle stages considered for the pMDI and DPI inhalers.

as ethanol and polyethylene glycol (PEG 1000), are also added in the pMDI formulation to increase drug solubility in HFC propellants, improve suspension behaviour or enhance valve function (Myrdal et al., 2014). These are all considered, as described further below.

2.2.1.1. Production of pMDI device. The pMDI device comprises a canister, an actuator, a valve, a mouthpiece and a cap. The canister is made of aluminium and, in this study, assumed to be coated with Teflon. The inhaler cap, mouthpiece, actuator and other parts are made of polypropylene, polyoxymethylene and polymethylacrylate (PMMA) as detailed in Table 1. The life cycle inventory data for the device have been obtained from a leading pharmaceutical company. The background data for materials and manufacturing have been sourced from the Ecoinvent V3.3 database (Ecoinvent, 2016).

2.2.1.2. Production of propellants. An overview of the processes for the production of different propellants is provided below.

i) HFC-134a ($C_2H_2F_4$) is produced in a two-step process from hydrofluoric (HF) acid and trichloroethylene (TCE) in the presence of a Cr_2O_3 catalyst:

$$C_2HCl_3 + 3HF \rightarrow C_2H_2ClF_3 + 2HCl$$

$$C_2H_2ClF_3 + HF \rightarrow C_2H_2F_4 + HCl$$

Lime, caustic soda and nitrogen are used as ancillary materials and HCl is produced as a co-product. The inventory data for the production and purification of the propellant are shown in Table 2. The data for the production of HFC-134a have been obtained from

Table 1
Inventory data for raw materials for the production of inhaler devices.

Size	pMDI	DPI
	100 doses (200 actuations) [a]	60 doses[a]
Aluminium	7.6 g	20 g
Teflon (for coating)	0.004 g	–
Polypropylene	14 g	1.3 g
Polyoxymethylene	0.4 g	7.7 g
Polymethylmethacrylate	0.006 g	–
Acrylonitrile-butadiene-styrene copolymer	–	35.6 g
Nylon	–	5 g
Polycarbonate	–	2.4 g
Polyvinylchloride	–	5 g

[a] pMDI: Pressurised metered-dose inhaler. DPI: dry powder inhaler (blister-based Diskus). The number of doses are based on a typical size of devices in the UK.

Table 2
Inventory data for the production of HFC-134a.

Inputs		Amount	Unit	Emissions	Amount	Unit
Production[a]						
Hydrofluoric acid		780	kg/t	Hydrofluoric acid	35	g/t
Trichloroethylene		1290	kg/t	Hydrochloric acid	32	g/t
Catalyst (Cr_2O_3)		1	kg/t	HFC-134a	106	g/t
Lime		48	kg/t	HFC-133a	86	g/t
Caustic soda (50%)		23	kg/t	Carbon monoxide	66	g/t
Nitrogen		22	kg/t	Trichloroethylene	100	g/t
Water		2	m^3/t	n-hexane	14	g/t
Electricity		830	kWh/t	Volatile organic compounds	389	g/t
Heat (natural gas and liquefied petroleum gas)		21,500	MJ/t			
Purification						
Nitrogen	15	kg/t	HFC-134a (fugitive)	770	g/t	
Electricity (MJ)	200	kWh/t				
Heat (MJ)	5300	MJ/t				

[a] Production of 1 tonne of HFC-134a produces 2.98 tonnes of HCl (36% w/w) as a co-product.

manufacturing plants in the USA and Japan, owned by Mexichem, a globally leading manufacturer of propellants. HFC-134a is further purified to the pharmaceutical grade (purity of ≥99.9% vol.) in the UK for use in inhalers (Fig. 2). The purification process also produces industrial grade HFC-134a as a co-product.

ii) HFC-227ea (C_3HF_7) is manufactured by hydrofluorination of hexafluoropropene (C_3F_6). The latter is produced through thermal conversion of tetrafluoroethylene (TFE) according to the following reactions:

$$3C_2F_4 \xrightarrow{Heat} 2C_3F_6$$

$$C_3F_6 + HF \rightarrow C_3HF_7$$

Table 3 provides the inventory data for the production of HFC-227ea, which have been obtained from literature (Banks et al., 1998). Energy use and other data for further processing of HFC-227ea from the industrial to pharmaceutical grade (purity of ≥99.99% vol.) are assumed to be similar to that of HFC-134a.

iii) HFC-152a ($C_2H_4F_2$) is made from vinyl chloride monomer and hydrofluoric acid as follows:

$$C_2H_3Cl + HF \rightarrow C_2H_4ClF$$

$$C_2H_4ClF + HF \rightarrow C_2H_4F_2 + HCl$$

Caustic soda, $SnCl_4$ catalyst and nitrogen are used as ancillaries. As can be seen from the second reaction above, this process also produces HCl as a co-product. Like HFC-134a, HFC-152a also has to be purified to the pharmaceutical grade (≥99.9% vol.). Table 4 details the inventory data for the production of HFC-152a, obtained from Mexichem.

Table 3
Inventory data for the production of HFC-227ea (Banks et al., 1998).

Inputs	Amount	Units	Emissions	Amount	Units
Production[a]					
Hydrofluoric (HF) acid	98	kg/t	Tetrafluoroethylene	13.3	kg/t
Tetrafluoroethylene	1123	kg/t	Hexafluoropropylene	29.9	kg/t
Heat (natural gas)	3250	MJ/t	HFC-227ea	7.5	kg/t
Purification					
Nitrogen	15	kg/t	HFC-227ea (fugitive)	770	g/t
Electricity	200	kWh/t			
Heat	5300	MJ/t			

[a] Data based on 90% yield of the HFC-227ea production process and 95% yield of the hexafluoropropene (intermediate) process (Banks et al., 1998).

Table 4
Inventory data for the production of HFC-152a.

Inputs	Amount	Units	Emissions	Amount	Units
Production[a]					
Hydrofluoric acid	638	kg/t	HFC-152a	447	g/t
Vinyl chloride monomer	997	kg/t			
Catalyst ($SnCl_4$)	1	kg/t			
Lime	48	kg/t			
Caustic soda (50%)	35	kg/t			
Nitrogen	53	kg/t			
Water	2	m^3/t			
Electricity	540	kWh/t			
Heat (natural gas)	3900	MJ/t			
Purification					
Nitrogen	15	kg/t	HFC-152a (fugitive)	770	g/t
Electricity	200	kWh/t			
Heat	5300	MJ/t			

[a] Production of 1 tonne of HFC-152a produces 1.5 tonnes of HCl (36% w/w) as a co-product.

2.2.1.3. Amount of propellant. The amount of propellant used in pMDIs varies widely due to several factors, including the size of inhaler, type of drug, type of propellant and the use of excipient and drug. pMDI inhalers are available in different sizes. The most commonly prescribed size in the UK for HFC-134a inhalers is 200 actuations (100 doses), while for HFC-227ea, it is 120 actuations (60 doses), as shown in Table 5. Although many pMDIs use a single actuation per dose, it is common for a pMDI dose to consist of two puffs (actuations). Table 6 provides the quantities of propellant for different inhalers, which have been obtained from the respective *Patient Information Leaflets* provided by drug manufacturers. In the base-case analysis, the weighted average quantities of the propellants in inhalers in the UK have been used. As can be seen in Table 6, these correspond to 166.7 mg/dose for HFC-134a and 162.7 mg/dose for HFC-227ea. Since there are no equivalent values for HFC-152a as it is still not used in inhalers, its required quantity per dose has been estimated based on the amount of HFC-134a currently used in pMDIs. Assuming an approximately constant number of moles of propellant in a pMDI, the equivalent amount of HFC-152a required would be 34% lower than that of HFC-134a, i.e. 110 mg/dose. Since the propulsion effect of the propellant is based on the volume of gas generated from a metered-dose of liquid propellant, an assumption of molar equivalence is correct.

2.2.2. Dry powder inhaler

DPIs, as their name suggests, contain and deliver the drug as a dry powder for respiratory therapy. The medication is either delivered through blisters, capsules or cartridges. There are numerous designs of devices currently available (Kou and Cao, 2016). In this study, a blister-based Diskus DPI is considered. The DPI device is made of different types of plastics, such as acrylonitrile butadiene styrene (ABS), polycarbonate, polypropylene, and polyoxymethylene, while blisters are made of polyvinyl chloride (PVC), aluminium foil and nylon. DPIs are also available in various sizes and the most common size prescribed in the UK is 60 doses (Table 5). The inventory data for the materials used for the manufacture of DPI in Table 1 are for a 60-dose Diskus inhaler, which have been obtained from the manufacturer.

2.2.3. Other data and assumptions

Propellant leakage in the manufacture of pMDI is assumed to be 1% (Enviros March 2000). After their usage, both types of inhaler are assumed to be disposed of as municipal solid waste (MSW). In the UK, 35% of non-recycled MSW is landfilled and 65% is incinerated with energy recovery (EC, 2018). It is assumed that all of the unused propellants are released into the atmosphere from the pMDIs during their usage or disposal.

Table 5
Annual usage of inhalers in the UK by type and size.[a].

Inhaler type	Size (actuations)	England (NHS England, 2017)	Scotland (NHS Scotland, 2017)	Wales (NHS Wales, 2017)	Northern Ireland (NHS Northern Ireland, 2017)	Total UK
HFC-134a	60	21,245	802	951	1084	24,142
	100	43,793	1275	690	250	46,108
	120	8,351,991	766,849	600,150	26,429	9,745,539
	200	35,827,775	3,681,420	2,392,031	1,401,577	43,303,003
	Sub total	*44,244,804*	*4,450,346*	*2,993,822*	*1,429,341*	*53,118,793*
HFC-227ea	112	16,355	2292	793	209	19,761
	120	776,708	75,062	88,054	122,990	1,062,934
	Sub total	*793,063*	*77,354*	*88,847*	*123,199*	*1,082,695*
DPI	30	1,040,074	79,764	132,970	97,344	1,350,182
	50	95,384	11,833	2989	2965	113,221
	60	6,135,470	940,289	305,555	301,142	7,682,516
	100	1,097,478	239,987	86,244	54,271	1,478,080
	120	3,463,433	354,575	261,910	108,502	4,188,540
	200	466,050	164,534	58,865	36,122	725,771
	Sub total	*12,297,889*	*1,790,982*	*848,533*	*600,346*	*15,538,310*
	Grand total	57,335,756	6,318,682	3,931,202	2,152,886	69,739,798

[a] Prescription data for the year 2016.

Table 6
Propellant quantities in pMDIs.

Drug	Brand	Size (actuations)[a]	No. of devices used per year in the UK[a]	Propellant (g/pMDI)[b]	Propellant (mg/dose)[b,c]	Other excipients[b]
HFC-134a						
Salbutamol	Generic	200	19,912,494	17.98	179.8	–
	Ventolin®	200	10,995,250	17.98	179.8	–
	Salamol®	200	2,421,630	16.54	165.4	Ethanol
	Airomir®	200	412,702	5.92	59.2	Oleic acid, ethanol
Ipratropium bromide	Generic	200	595,194	10.90	109.0	Water, citric acid, ethanol
	Atrovent®	200	119,361	10.90	109.0	Water, citric acid, ethanol
Beclometasone dipropionate	Qvar®	200	1,877,413	11.18	111.8	Glycerol, ethanol
	Clenil®	200	6,830,174	11.18	111.8	Glycerol, ethanol
Beclometasone/formoterol	Fostair®	120	3,510,001	11.16	186.0	HCl, ethanol
Fluticasone propionate	Seretide®	120	3,278,659	11.97	199.5	–
	Others	120	2,227,070	11.97	199.5	Ethanol
Salmeterol	Neovent®	120	577,165	11.97	199.5	Ethanol, E322
	Others	120	202,200	11.97	199.5	Ethanol, E322
Ciclesonide	Alvesco®	120	31,504	8.42	140.3	Ethanol
	Generic	120	3059	8.42	140.3	Ethanol, E322
	Alvesco®	60	24,261	5.61	187.1	Ethanol, E322
Formoterol Fumarate	Atimos Modulite®	100	45,756	8.42	168.4	Ethanol
Weighted average					*166.7*	
HFC-227ea						
Fluticasone propionate	Flutiform®	120	1,055,634	9.64	160.7	Ethanol, sodium cromoglicate
Budesonide	Symbicort®	120	7226	10.15	169.2	Macrogol 1000, K30
Sodium cromoglicate	Intal®	112	12,187	15.31	273.4	Macrogol 600, levomenthol, K30
Nedocromil sodium	Tilade®	112	7412	15.31	273.4	PEG 600, K30
Weighted average					*162.7*	

[a] Based on prescription data in the UK for the year 2016.
[b] Obtained from *Patient Information Leaflets* provided by respective drug manufacturers.
[c] The recommended dose depends on various factors, such as the type of respiratory ailments, severity of the disease, age of the patient, strength of the drug, etc. For most of the conditions, generally two puffs (actuations) per dose are recommended but the dosage can vary from one puff (for mild conditions) to four puffs (for severe conditions).

Containers and packaging materials for the raw materials and propellants are not considered, since they are reused. Secondary packaging of inhalers is also excluded. The transport distances for the raw materials have been estimated based on their origin and transport modes provided by Mexichem. A transport distance of 200 km has been assumed for the transport of inhalers from a factory to a pharmacy. Ancillary materials and end-of-life waste are assumed to be transported over a distance of 100 km.

The impacts of the pharmaceutical and industrial grades of HFCs have been allocated on an economic basis. According to the data from industry, the pharmaceutical-grade HFCs have a 30% higher market value than the industrial grade. It is assumed that HCl co-produced with HFCs has no economic value and hence all the burdens have been allocated to the HFCs. However, since the price of HCl fluctuates with demand, the economic allocation using the average annual price is considered in the sensitivity analysis to assess the influence of the above assumption on the results.

2.3. Impact assessment

The GaBi 8.7 software (Thinkstep, 2018) has been used for system modelling and estimating the impacts, applying the ReCiPe 2016 V1.1 impact assessment method (Huijbregts et al., 2017). The following 14 impact categories are considered: global warming potential (GWP), fossil depletion (FD), metal depletion (MD), terrestrial acidification (TA), freshwater eutrophication (FE), marine eutrophication (ME), human toxicity – cancer (HTc) and human toxicity – non-cancer (HTnc), freshwater ecotoxicity (FET), marine ecotoxicity (MET), terrestrial ecotoxicity (TET), ozone depletion (OD), photochemical oxidants formation – human health (POFh) and photochemical oxidants formation – ecosystem (POFe). For a brief overview of these impacts, see the Supplementary Information.

3. Results and discussion

3.1. Environmental impacts of inhalers

This section discusses and compares the impacts of individual inhalers, based on the functional unit of 1 dose. The total impacts for each inhaler type are presented in Fig. 3, with the contribution of different life cycle stages given in Fig. 4. As can be seen in Fig. 3, the HFC-152a pMDI has the lowest impacts for ten impact categories, DPI for two and HFC-134a and HFC-227ea for the remaining two. However, the DPI is the worst option for eight impacts, followed by the HFC-227ea pMDI with six highest impacts. These findings are discussed below in more detail for each impact category in turn.

3.1.1. Global warming potential (GWP)

As can be seen in Fig. 3, the GWP of 1 dose of the HFC-227ea pMDI is the highest, estimated at 697 g CO_2 eq. This is 34 and 13 times higher than the GWP of the HFC-152a and HFC-134a inhalers, respectively. The lowest impact is found for the DPI with 9 g CO_2 eq./dose, 2.4 times lower than the GWP of the HFC-152a inhaler, the best pMDI option.

For the pMDIs, the main hotspot is the emission of propellants to the atmosphere during the use stage (Fig. 4), contributing 98% to the GWP of the HFC-134a inhaler and 90% for the impact of the HFC-152a and HFC-227ea inhalers. This is due to the relatively high GWP of the propellants, which are 167 to 1550 times higher than

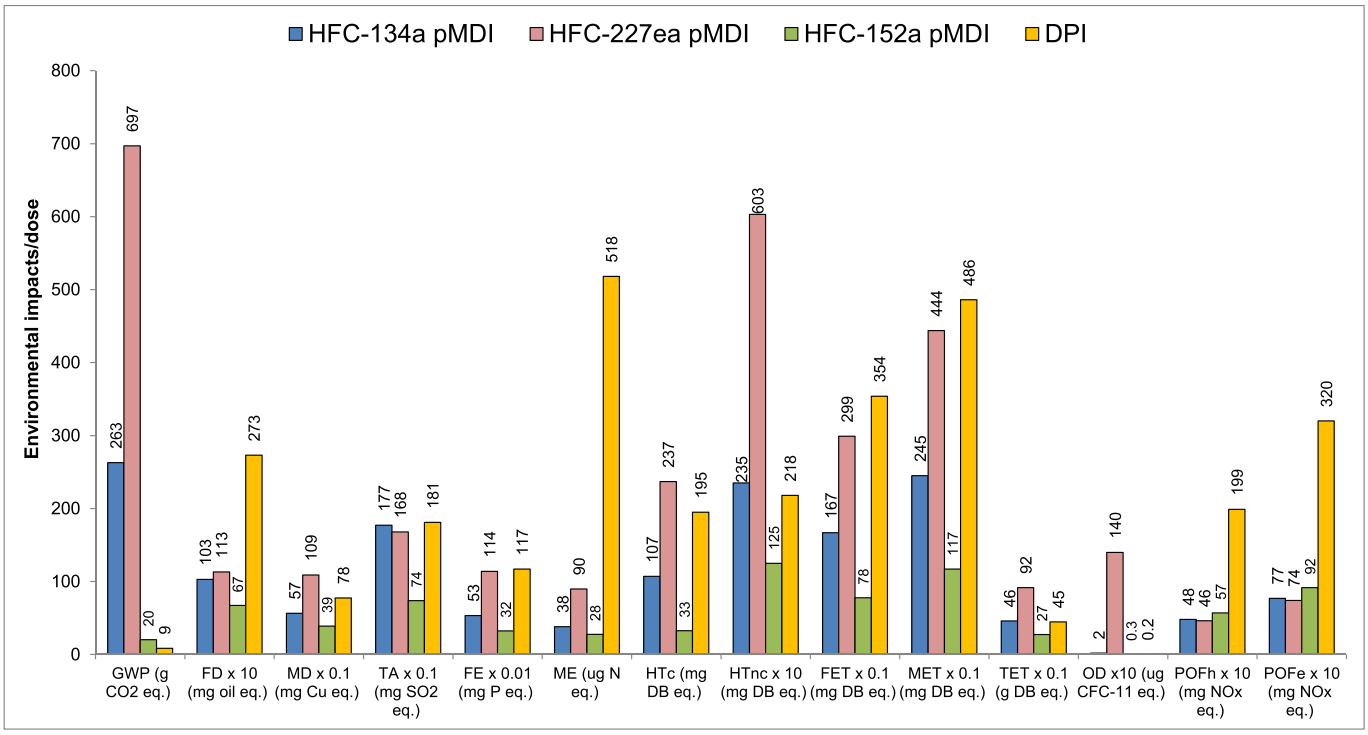


Fig. 3. Life cycle environmental impacts of inhalers.
[pMDI: pressurised metered-dose inhaler. DPI: dry powder inhaler. GWP: global warming potential; FD: fossil depletion; MD: metal depletion; TA: terrestrial acidification; FE: freshwater eutrophication; ME: marine eutrophication; HTc: human toxicity cancer; HTnc: human toxicity non-cancer FET: freshwater ecotoxicity; MET: marine ecotoxicity; TET: terrestrial ecotoxicity; OD: ozone depletion; POFh: photochemical oxidants formation – human health; POFe: photochemical oxidants formation - ecosystem. Some impacts have been scaled to fit and should be multiplied by the factor shown on the x-axis to obtain the original values.]

that of CO_2 (Table S1). For the DPI, the raw materials are the dominant contributors (70%), followed by the production process (22%). The contributions of transport and waste disposal are negligible across the inhalers.

3.1.2. Fossil and metal depletion (FD and MD)

The HFC-152a inhaler has the lowest depletion of fossil resources, estimated at 0.7 g oil eq./dose; this is 75% lower than that of the DPI, which is the worst option for this impact, and 35–40% lower than the pMDIs with the other two types of propellant. The raw materials are the major contributor to FD for all the inhalers.

The HFC-152a pDMI also has the lowest metal depletion (3.9 mg Cu eq./dose) while the HFC-227ea variant is the worst alternative (10.9 mg Cu eq./dose). The raw materials used for the production of propellants and the canister are the main hotspots for the pMDIs. In the case of DPI, beside the raw materials, the production process and waste disposal are also significant contributors (Fig. 4).

3.1.3. Terrestrial acidification (TA)

TA of the HFC-152a inhaler, estimated at 7.4 mg SO_2/dose, is 55–60% lower than all the other inhalers considered. Raw materials are also the main hotspot for this impact across the inhalers. In the case of HFC-152a, the production of HF accounts for 50% of the impact, while for the HFC-227ea, TFE contributes to 76% of the total. For the HFC-134a, HF and TCE cause 38% of TA each. The main contributors to the TA of the DPI are plastic materials (ABS and PVC) used for the production of the device and aluminium for the blister pack. The contribution of heat and electricity used in the production process is also significant (35%) for the DPI.

3.1.4. Freshwater and marine eutrophication (FE and ME)

Both of these impacts are the highest for the DPI and the lowest for the HFC-152a inhaler. The FE of the HFC-152a pMDI is around 3.5 times lower than that of the HFC-227ea pMDI and DPI. This difference is even starker for ME, for which the DPI has 20 times higher impact than the HFC-152a inhaler. The main reasons for the high FE of the DPI are the phosphate emissions from the process wastewater and for the ME, nylon and ABS.

3.1.5. Human toxicity potential - cancer and non-cancer (HTc and HTnc)

The HFC-152a inhaler is also the best option for these impacts, with HTc and HTnc around five and seven times lower, respectively, than the worst alternative – HFC-227ea. The DPI follows closely the HFC-227ea for HTc, with the impact six times higher than that of the HFC-152a inhaler. For HTnc, the DPI and HFC-134a have a similar impact, around 40% higher than HFC-152a. Raw materials are the main hotspots for all the inhalers; for the DPI, manufacture (injection moulding) of the device is also a significant contributor (Fig. 4).

3.1.6. Ecotoxicity potentials (FET, MET and TET)

The HFC-152a pMDI has the lowest impacts for all three categories. The DPI is the worst alternative for FET and MET, followed closely by HFC-227ea. In the case of TET, HFC-227ea has a three times higher impact than HFC-152a and two times greater than DPI and HFC-134a. Raw materials are the main hotspot for all these impacts across the inhalers. For the DPI, injection moulding is also an important contributor.

3.1.7. Ozone layer depletion (OD)

The lowest OD is estimated for the HFC-152a pMDI, 420 times

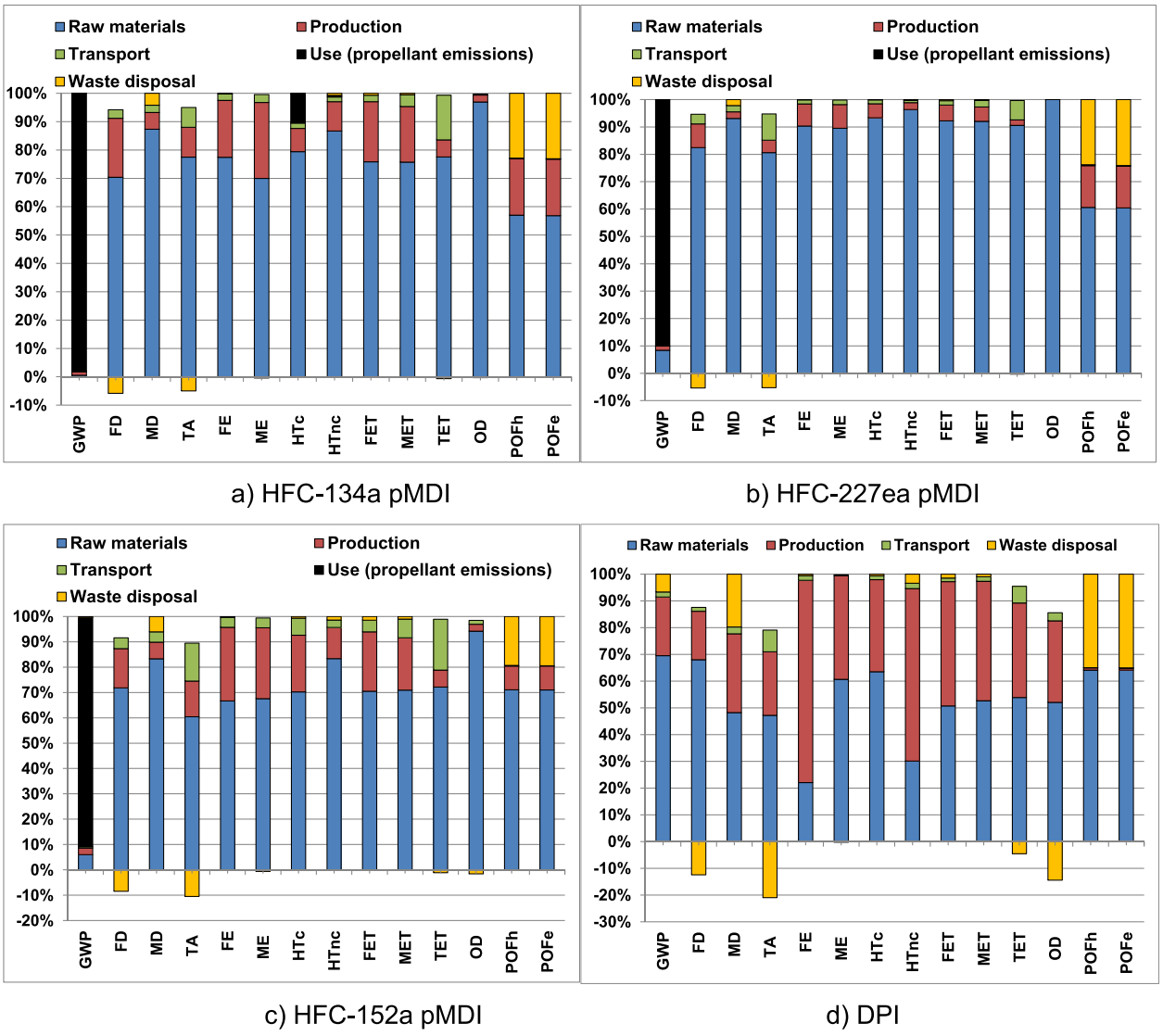


Fig. 4. Contribution of different life cycle stages to the impacts of inhalers. [For the impacts nomenclature, see Fig. 3].

lower than the highest value estimated for the HFC-227ea inhaler. Its impact is also a factor of five smaller than that of HFC-134a. The high OD for these two inhalers is due to halogenated organic compounds emitted during the production of tetrafluoroethylene and trichloroethylene, respectively, used in the manufacture of the propellants.

3.1.8. Photochemical oxidants formation – human health and ecosystem (POFh and POFe)

Both POF impacts are 3.5–5 times higher for the DPI than for the other inhalers (Fig. 3). This is largely due to the release of waste heat from the raw materials production and waste disposal processes. The HFC-227ea inhaler has the lowest POF impacts, followed closely by HFC-134a.

3.1.9. Sensitivity analysis

The sensitivity analysis explores the effect on the results of the following three aspects:

- the amount of propellants used in inhalers;
- using system expansion instead of economic allocation for pharmaceutical and industrial grades of HFCs; and
- using economic allocation between HFCs and HCl instead of allocating all impacts to HFCs.

3.1.9.1. Amount of propellant used in inhalers. As indicated in Table 6, the amount of propellants in the currently available inhalers varies significantly, either due to the size or design of the device or due to formulation differences. Given the significant contribution of the propellants to the impacts, the sensitivity analysis considers the effect on the results of different quantities of propellants in inhalers. As mentioned earlier, the weighted average amounts of propellants used in inhalers in the UK have been considered in the base case, which is equivalent to 166.7 mg of propellant/dose for the HFC-134a pMDI. However, as shown in Table 6, some inhalers contain much less propellant. For example, Airomir® has only 59 mg of HFC-134a/dose. On the other hand,

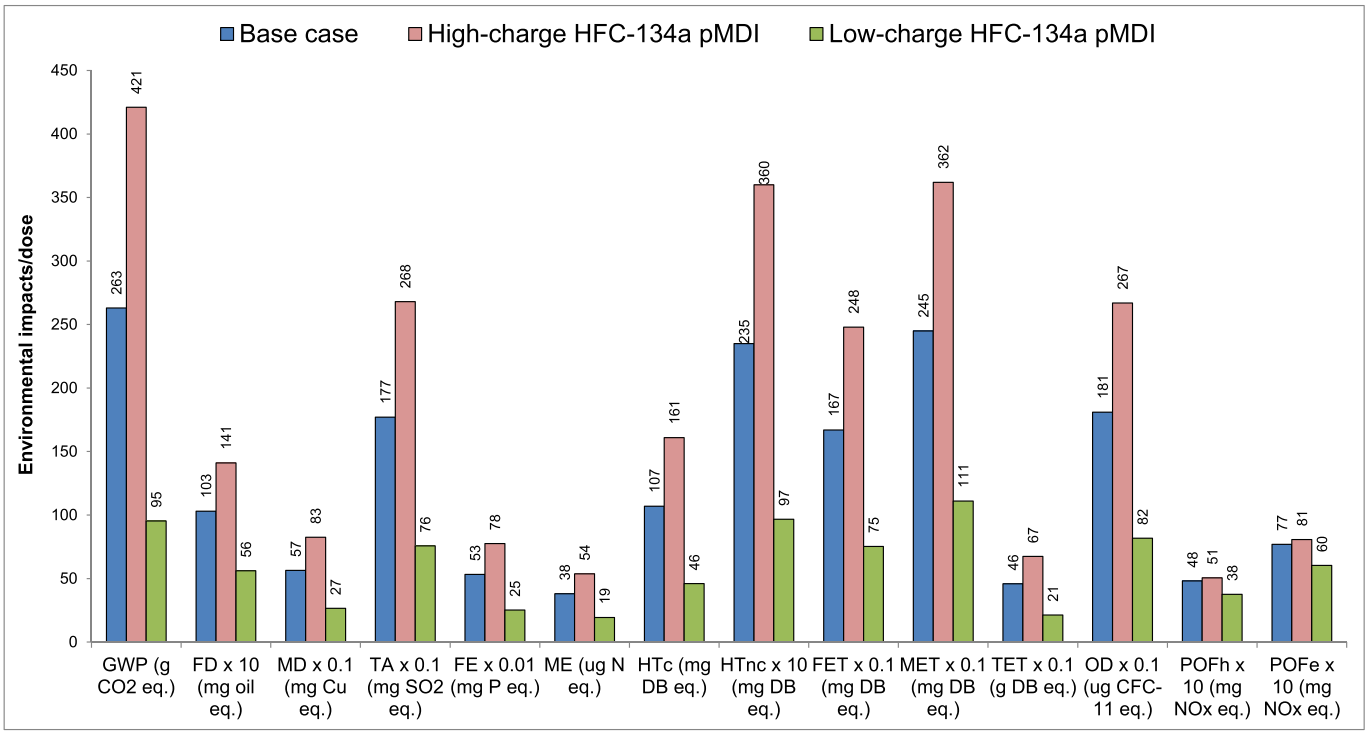


Fig. 5. The effect on impacts of the amount of propellant in inhalers.
[Some impacts have been scaled to fit. To obtain the original values, multiply by the factor in brackets shown on the x-axis for relevant impacts. For the impacts nomenclature, see Fig. 3].

small-size Ventolin® inhaler with 30 doses[1] uses 267 mg of HFC-134a per one dose (GlaxoSmithKline, 2009). Therefore, these two values, which represent the minimum and maximum values in the range of the quantities of HFC-134a found on the market are considered within the sensitivity analysis. In the case of HFC-227ea, the minimum and maximum values of propellant for the inhalers found on the market vary from 161 mg to 273 mg (Table 6). These values are also considered in the sensitivity analysis.

As shown in Fig. 5, if the amount of propellant is increased by 60% on the base case ('high-charge pMDI' as in the small-size Ventolin®), all impacts increase by 35–60%, except for the two POF impacts which go up by 5%. However, if the amount of propellant in pMDIs is reduced by 65% ('low-charge pMDI' as in Airomir®), the impacts decrease by 22–64%. The effect on the impacts is much smaller for a low-charge HFC-227ea pMDI (not shown in a figure for brevity), reducing the impacts by only 0.2–2% – this is due to a small difference (1%) between the base-case and the minimum charge found on the market. However, increasing the charge of HFC-227ea by 67% increases the impacts by 12–68% compared to the base case. Therefore, most impacts are highly sensitive to this variable, suggesting that they can be mitigated by reducing the amount of propellant in inhalers.

3.1.9.2. System expansion instead of economic allocation. In the base case, economic allocation has been used to allocate the environmental burdens between the pharmaceutical and industrial grades of HFCs in the purification process. To assess the influence of this assumption on the results, system expansion or the 'avoided burdens' approach is considered in the sensitivity analysis. For this purpose, it is assumed that the environmental burdens of industrial grade HFC are similar to the burdens of HFC before the purification step. These burdens are credited for the production of industrial grade of HFC. In other words, all energy use and emissions of the purification process are allocated to the pharmaceutical grade HFC. The results in Fig. 6 show that this assumption leads to a very small change in the impacts (0.1–7%). Hence, the choice of allocation method has no significant effect on the results.

3.1.9.3. Economic allocation between HFCs and HCl. It has been assumed in the base case that HCl co-produced with HFC-134a and HFC-152a has no economic value and hence all the burdens have been allocated to the HFCs. In the sensitivity analysis, economic allocation is considered based on the average factory gate prices of HFC-134a, HFC-152a and HCl (confidential). On average, HFC-134a and HFC-152a are 102 and 92 times more valuable than HCl (36%), respectively.

As can be seen in Table 7, most impacts of HFCs change by 1%–3%, with the exception of GWP, POFh and POFe which are not affected. For HFC-152a inhaler, OD also remains unchanged. Thus, the effect on the results of allocating the impacts to HCl is very small.

3.1.10. Uncertainty analysis

The uncertainty analysis has been carried out to examine the reliability of the results against a likely range of variations in different inventory parameters. These include the quantities of raw materials and energy used in the production of inhaler devices, energy used and emissions during the production of propellants, the quantity of propellants used in pMDIs and the transport of raw materials. Since the data on the variations in the above-mentioned parameters are not available, an arbitrary variation of ±25% from the base-case values of the parameters has been applied.

[1] Not shown in Table 6 as this size was not available that year (2016).

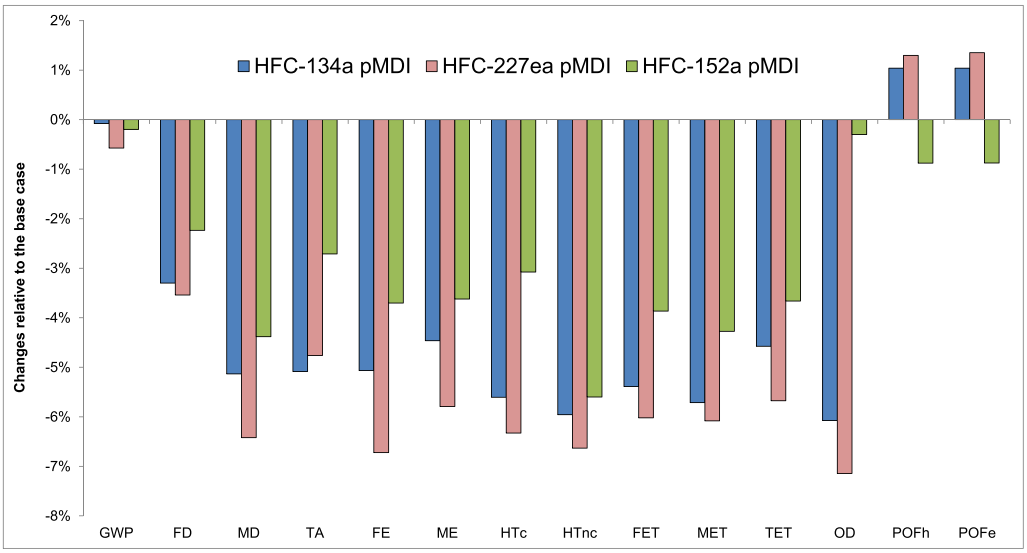


Fig. 6. The effect on impacts of using the 'avoided burdens' approach compared to economic allocation.
[For the impacts nomenclature, see Fig. 3].

Table 7
The effect on impacts of HFC-134a and HFC-152a inhalers of using economic allocation for HCl.

Impacts	HFC-134a pMDI			HFC-152a pMDI		
	No allocation for HCl (base case)	Economic allocation	Change relative to the base case (%)[a]	No allocation for HCl (base case)	Economic allocation	Change relative to the base case (%)[a]
GWP (g CO_2 eq./dose)	263.0	263.0	0%	20.3	20.3	0%
FD (mg oil eq./dose)	1030.0	1020.0	−1%	671.0	667.0	−1%
MD (mg Cu eq./dose)	5.7	5.5	−2%	3.9	3.8	−1%
TA (mg SO_2 eq./dose)	17.7	17.3	−2%	7.4	7.3	−1%
FE (μg P eq./dose)	533.0	521.0	−2%	324.0	321.0	−1%
ME (μg N eq./dose)	38.1	37.4	−2%	27.6	27.4	−1%
HTc (mg DB eq./dose)	107.0	104.0	−3%	32.5	32.2	−1%
HTnc (mg DB eq./dose)	2350.0	2290.0	−3%	1250.0	1230.0	−2%
FET (mg DB eq./dose)	16.7	16.3	−2%	7.8	7.7	−1%
MET (mg DB eq./dose)	24.5	23.9	−2%	11.7	11.6	−1%
TET (g DB eq./dose)	4590.0	4500.0	−2%	2730.0	2700.0	−1%
OD (μg CFC-11 eq./dose)	18.1	17.6	−3%	3.3	3.3	0%
POFh (mg NOx eq./dose)	481.0	479.0	0%	569.0	567.0	0%
POFe (mg NOx eq./dose)	770.0	768.0	0%	915.0	911.0	0%

[a] The negative sign denotes reduction in impacts. For the impacts nomenclature, see Fig. 3.

A Monte Carlo simulation with 10,000 iterations has been performed to generate probabilistic values for the impacts of all four inhalers considered in the study. The box plots in Fig. 7 show the interquartile ranges along with the 10th and 90th percentile ranges. It can be seen that for the pMDIs, the impacts deviate by ±12−22% relative to the base case. The greatest variation can be observed for GWP for HFC-152a (±17%) and HFC-134a (±20%). The other significant deviations (±22%) are found for the HT and POF impacts of the DPI.

Despite these variations in the impacts, the estimated uncertainty ranges (whisker bars in Fig. 7) for the HFC-152a inhaler do not overlap with the other three types of inhaler for any of the ten impact categories for which it has lower impacts. This suggests a high confidence in the findings that the HFC-152a inhaler has lower environmental impacts in those ten categories compared to the other inhalers.

3.1.11. Comparison of results with literature

To validate the findings, this section compares the results for HFC-134a, HFC-227ea and dry powder inhalers obtained in the current work with other studies. Comparison of the results for HFC-152a pMDI is not possible as this is the first time an LCA study has been carried out for this type of inhaler.

As mentioned in the introduction, three other studies have

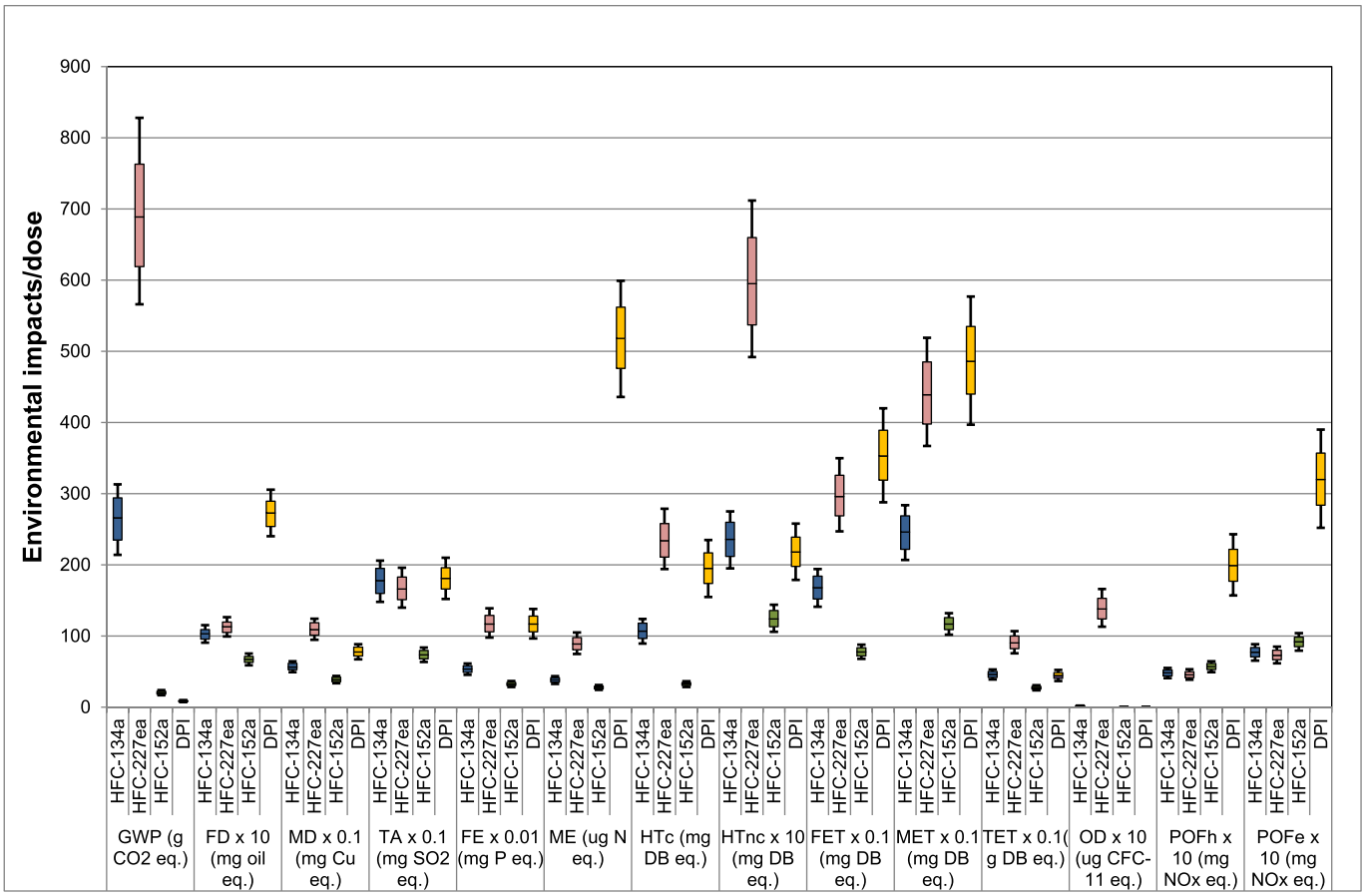


Fig. 7. The results of the uncertainty analysis.
[Box plots represent the 1st and 3rd quartiles and the whiskers show the range between the 10th and 90th percentile. Some impacts have been scaled to fit. To obtain the original values, multiply by the factor in brackets shown on the x-axis for relevant impacts. For the impacts nomenclature, see Fig. 3].

Table 8
Comparison of results with literature.

Source	HFC-134a pMDI (g CO_2 eq./dose)	HFC-227ea pMDI (g CO_2 eq./dose)	DPI (g CO_2 eq./dose)	Comments
This study	263	697	9	–
UNEP (2014)	200–300	600–800	8–60	–
GlaxoSmithKline (2014)	280–340	–	10.4	For DPI, the GWP is 20 g CO_2 eq./dose, including the active pharmaceutical ingredients (API). The contribution of API to GWP is 48%.
Goulet et al. (2017)	97	–	–	ProVent® inhaler with 6 g of propellant for a 200-dose pMDI.

assessed the GWP of inhalers and their results are summarised in Table 8. As can be observed from the table, the results of this study are congruent with the UNEP (2014) and GlaxoSmithKline (2014) assessments.

However, the GWP of the HFC-134a inhaler in Goulet et al. (2017) study is much lower. This is because they considered ProVent® inhaler, which uses 60% less propellant, hence a direct comparison cannot be made. However, the results agree very well with the estimates in the sensitivity analysis for Airomir®, a similar type of inhaler (97 vs 95 g CO_2 eq./dose). Therefore, it can be concluded that the impacts estimated here for the existing inhalers fall within the ranges found in the literature.

3.2. Environmental impacts of inhalers at the UK level

This section analyses the environmental impacts of inhalers used in the UK based on the results presented in the previous sections and the quantities of the inhalers prescribed annually. The data for the latter were obtained from the NHS in England, Scotland, Wales and NI (Table 5). As can be seen in Fig. 8, the annual GWP of inhalers amounts to 1.34 Mt CO_2 eq. Considering that the total GHG emissions of the NHS in England and Scotland are 26.6 Mt CO_2 eq./yr (Sustainable Development Unit, 2016) and 2.63 Mt CO_2 eq./yr (NHS Scotland, 2009), respectively, the inhalers account for around 4.3% of the NHS emissions in England and Scotland. The data for GHG emissions for the NHS in Wales and Northern Ireland are not available. The contribution of inhalers to the UK's GHG emissions is around 0.3%. Although this percentage appears to be small, it is equivalent to the annual GHG emissions from 610,000 diesel cars in the UK.[2] The other environmental

[2] GHG emissions from an average diesel car: 177.5 g CO_2 eq./km (DEFRA, 2018); annual mileage per car: 12,400 km (Department for Transport, 2018).

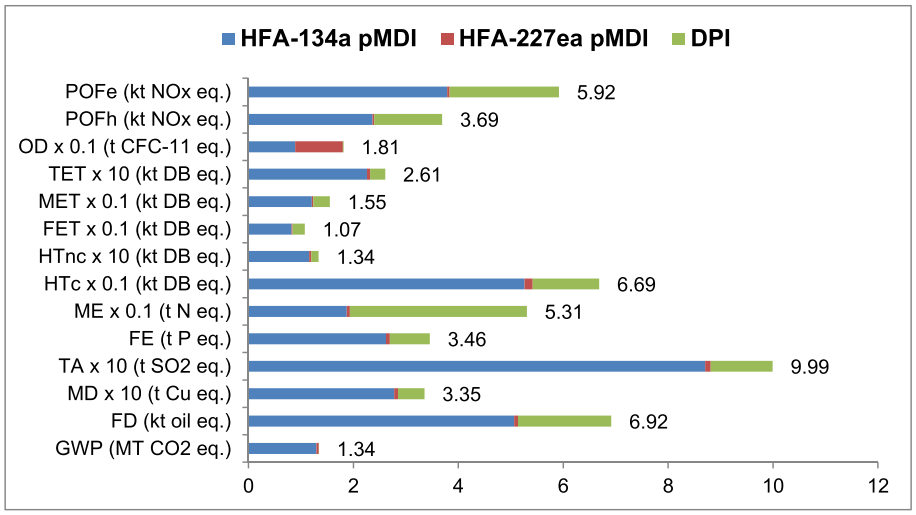


Fig. 8. Environmental impacts of the annual usage of inhalers in the UK.
[All impacts are expressed per year. Some impacts have been scaled to fit. To obtain the original values, multiply by the factor in brackets shown on the x-axis for relevant impacts. For the impacts nomenclature, see Fig. 3].

impacts cannot be put into context as their data, both at the NHS and UK levels, are not available.

Fig. 8 also shows that the HFC-134a inhalers have the highest contribution to all impact categories, except ME and OD. These two impacts are respectively mainly due to DPIs (60%) and HFC-227ea and HFC-134a (50% each).

To identify opportunities for reducing the impacts associated with the annual usage of inhalers, the following seven possible future scenarios are considered:

- S-1: Replacement of both HFC-134a and HFC-227ea with HFC-152a pMDIs
- S-2: Replacement of all pMDIs with DPIs
- S-3: Reduction in propellant usage in pMDIs by 60% (as in some current inhalers)
- S-4: Recovery of propellants from used pMDIs
- S-5: Combination of S-1, S-3 and S-4 (replacement of both HFC-134a and HFC-227ea in pMDI by HFC-152a, reduction in propellant usage in pMDI by 60% and recovery of HFC-152a from used pMDIs)
- S-6: Use of HFC-134a in all pMDIs (replacement of HFC-227ea with HFC-134a pMDIs)
- S-7: Combination of S-3, S-4 and S-6 (all pMDIs with HFC-134a, reduction in propellant usage in pMDI by 60% and recovery of HFC-134a from used pMDIs).

The results in Table 9 suggest that by replacing current propellants in pMDI with HFC-152a (S-1), the GWP and OD would be reduced by 90%–92%. This would also lead to large reductions (>40%) in acidification, ecotoxicity and human toxicity impacts; the other impacts would be 10%–37% lower. The only exceptions are the POF impacts which would increase in this scenario by 12%.

Replacing all pMDIs with DPIs (S-2) would achieve even higher reductions (94–96%) for GWP and OD than in S-1. However, this would happen at the expense of several other impacts which would increase significantly. The most notable increases would be for ME,

Table 9
Comparison of different scenarios with the current situation[a].

	S-1	S-2	S-3	S-4	S-5	S-6	S-7
Global warming potential	-92%	-96%	-59%	-10%	-97%	-2%	-64%
Fossil depletion	-26%	122%	-34%	-13%	-51%	0%	-41%
Metal depletion	-27%	30%	-44%	-15%	-64%	-1%	-54%
Terrestrial acidification	-51%	2%	-48%	-4%	-67%	0%	-48%
Freshwater eutrophication	-31%	91%	-40%	-5%	-52%	-1%	-40%
Marine eutrophication	-10%	450%	-18%	3%	-16%	-1%	-13%
Human toxicity (cancer)	-57%	64%	-45%	-8%	-69%	-1%	-48%
Human toxicity (non-cancer)	-43%	-8%	-50%	-3%	-65%	-2%	-49%
Freshwater ecotoxicity	-42%	86%	-42%	2%	-51%	-1%	-35%
Marine ecotoxicity	-42%	77%	-42%	2%	-51%	-1%	-35%
Terrestrial ecotoxicity	-37%	-4%	-47%	-4%	-59%	-1%	-45%
Ozone depletion	-90%	-94%	-56%	-6%	-90%	-50%	-75%
Photochemical oxidants formation (human health)	12%	204%	-19%	-8%	-12%	0%	-17%
Photochemical oxidants formation (ecosystems)	12%	205%	-18%	-8%	-12%	0%	-17%

[a] The negative sign denotes reduction in impacts.

Legend: ≥50% reduction | 1%-49% reduction | 1%-49% increase | ≥50% increase

POF and FD, which would be 2–6 times higher than currently.

Using 60% less propellant per dose (S-3) would result in a 59% and 56% reduction in GWP and OD, respectively (Table 9). All other impacts would also be reduced, ranging from 18% for ME to 50% for HT (non-cancer).

It is estimated that about 10% of propellant is left in used pMDIs (Enviros March, 2000), which can be recovered and reused in refrigeration or other industries. GSK has set up a scheme called "Complete the Cycle" in the UK in 2011 to recover the remaining propellant from used inhalers (GlaxoSmithKline, 2011). Therefore, it is assumed in S-4, that in the future all used pMDIs will be collected and the leftover propellants will be treated and reused in industrial applications. It is also assumed that plastic and aluminium components of pMDI are recycled. This would result in the reduction of all impacts compared to the base case; however, the reductions would be relatively small. The most notable reductions are found for GWP, FD and MD, which would be reduced by 10–15%. The reductions in the other impacts would be smaller (3%–8%).

As shown in Table 9, combining S-1, S-3 and S-4 in S-5 would reduce all the impacts by 12% (POF) to 97% (GWP). For the latter, the annual GHG savings would be equivalent to taking 590,000 diesel cars off the road. Furthermore, replacing all HFC-227ea with HFC-134a inhalers (S-6) would result in a very small reduction ($\leq$2%) in all impacts except OD, which would be reduced by 50% (Table 9). In scenario S-7, which combines S-3, S-4 and S-6, the highest reduction also occurs for OD (75%). This is followed by GWP and MD which are reduced by 64% and 54%, respectively. The reductions in other impacts vary from 13% for ME to 49% for HT (non-cancer).

4. Conclusions

This study has evaluated the life cycle environmental impacts associated with pMDI and DPI, two most common types of inhaler globally. Three different propellants have been considered for the pMDIs: two used at present (HFC-134a and HFC-227ea) and one currently under consideration by the pharma industry (HFC-152a). The results suggest that pMDIs with HFC-152a have the lowest impacts for ten out of 14 categories considered. DPIs are the best option for GWP and OD while HFC-134a and HFC-227ea have the smallest POF impacts. However, the DPIs are the worst option for eight impacts, followed by the HFC-227ea pMDIs with six highest impacts. The results of the uncertainty analysis show that these findings are robust over the broad range of the influencing parameters.

The annual use of inhalers in the UK generates GHG emissions equivalent to 1.34 Mt CO_2 eq., largely due to the HFC-134a inhalers. This represents 4.3% of the NHS and 0.3% of national emissions. The results of the scenario analysis show that replacing HFC-227ea and HFC-134a propellants by HFC-152a in pMDIs would result in a 92% reduction in GWP and OD. Most other impacts would also decrease significantly. However, the successful deployment of HFC-152a propellants in pMDIs will depend on safety and formulation behaviour, which are still being investigated.

Although DPI considered in this study has the lowest GWP and OD, switching from pMDIs to DPIs could cause a significant increase in several other impacts, including human toxicity, marine eutrophication and fossil depletion. Moreover, it is not yet technically or economically feasible to replace completely HFC-based pMDIs, due to cost, technical and patient-acceptability factors. Since replacing propellants or pMDIs requires further research and development, pharmaceutical companies should consider these measures as part of a long-term strategy. In the short-term, they should implement already tried and tested measures for minimising propellant emissions, including reducing the size of metering valves to reduce propellant usage per dose and increasing propellant recovery for spent or partly-used pMDIs. Such actions will continue to be beneficial should HFC-152a be introduced on a commercial basis in the future.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclepro.2019.117733.

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