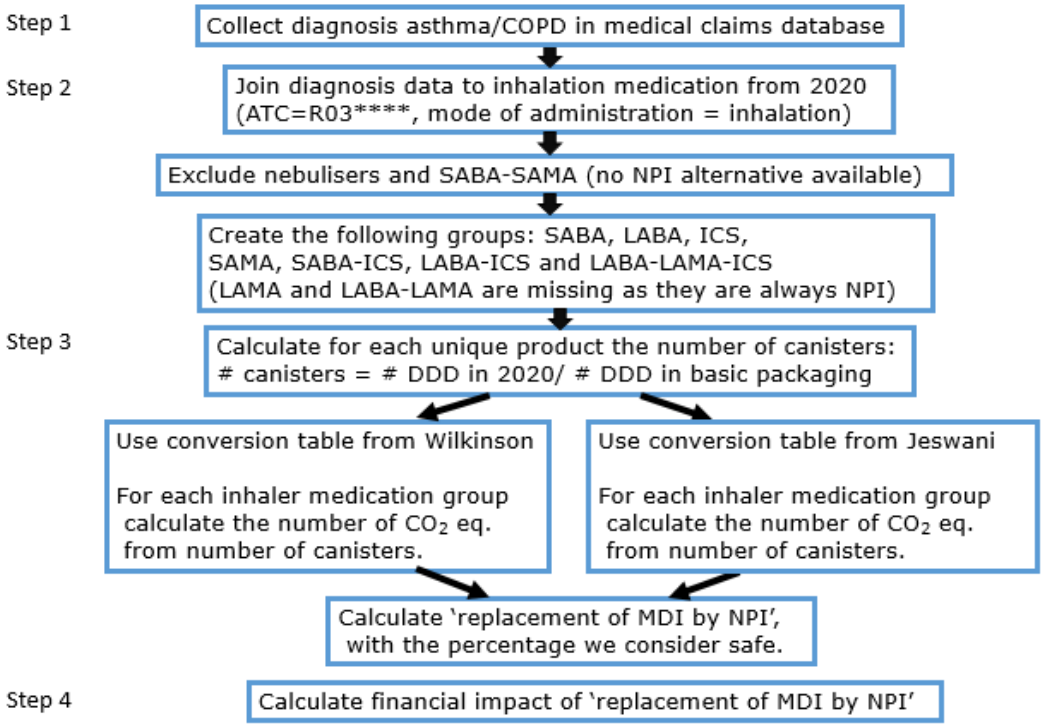
Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Introduction

We calculate the impact of replacing pressurized metered-dose inhalers (pMDIs) by non-propellant inhalers (NPIs), a group consisting of both dry powder inhalers (DPIs) and soft mist inhalers, on greenhouse gas emissions in Dutch respiratory healthcare. The major steps of our method are shown in Figure 1.

Figure 1. Steps to calculate the impact of conversion of pMDI to NPI



Our data-analysis protocol is:

Step 1: Collect diagnoses asthma/COPD from medical claims database

Use the DIS database (DBC Informatie Systeem | Diagnosis-Treatment Combination Information system) to collect the identifiers and diagnoses of patients that received care for asthma or COPD between 2012 and 2020. The DIS database is a medical claims database covering all medical care delivered to Dutch citizens, including private health

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

care. The independent government body Dutch Health Care Authority (Nederlandse Zorgautoriteit) owns this database. The reason for this initial step is to find out how many pMDI DDDs[1] were prescribed for patients with severe COPD, as guidelines do not consider them eligible for DPI. Also, we wanted to know how pMDIs are distributed between asthma and COPD. The DIS database does not contain all primary care diagnoses.

Step 2: Join these diagnoses to the inhalation medication prescribed in 2020

The GIP database (Genees- en hulpmiddelen Informatie Project | Medicines and medical devices Information Project) contains all prescriptions of all Dutch citizens from pharmacies since about 1985. The Dutch National Health Care Institute (Zorginstituut Nederland) is the owner of this database. Use the GIP database to select all medication where the ATC-code starts with 'R03', the mode of administration is 'inhalation' and the year is 2020. Increase all numbers with 3%, because a few small health insurance companies do not deliver claims data. These missing data represent 3% of the claims volume.

Exclude the nebulizers since they don't contain propellants and because they are usually not an appropriate alternative for a pMDI due to their size and dependency on electrical energy.

Label 'soft mist inhalers' and 'DPIs' as non-propellant inhalers (NPIs) since they do not contain propellants and may be considered an alternative to pMDI.

Exclude the SABA-SAMA medication, because there are no NPIs containing both SABA and SAMA and they can't be replaced properly. We considered all replacements from pMDI to NPI to be acceptable as long as the medication group stays the same and the patient doesn't end up with more inhalers. Because there is no NPI SABA-SAMA available, replacing a pMDI SABA-SAMA by a NPI SABA plus a NPI SAMA, would lead to an extra inhaler. This, we did not consider acceptable for replacement. We believed it is not necessary to keep the ATC-code the same during a replacement. E.g., we considered replacing any pMDI SABA by any NPI SABA to be acceptable, since the medication group remained unchanged.

[1] The Defined Daily Dose (DDD) is an international technical unit of measuring drug consumption defined as the assumed average maintenance dose per day for a drug used for its main indication in adults (source: https://www.who.int/tools/atc-ddd-toolkit/about-ddd).

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Create the following medication groups, allowing replacement within each group: SABA, LABA, ICS, SAMA, SABA-ICS, LABA-ICS and LABA-LAMA-ICS. LAMA and LABA-LAMA are missing from the list of inhalation medication with propellants, as they are always delivered by NPI.

Step 3: Calculate the carbon dioxide impact of replacement of pMDI by NPI

Calculate the number of canisters for each specific inhalation medication product. The number of DDDs in basic packaging is one of the database fields of the GIP database.

Calculate the carbon dioxide equivalent (CO_2 eq.) per type of canister. Do this once by using the conversion table from Wilkinson et al.[2] and once by using the conversion table from Jeswani & Azapagic.[3] Because the two conversion tables deliver different results, we choose to use both tables in order to create a range. Not all types of canisters were mentioned in the two conversion tables. Therefore we added some assumptions to the tables and marked them. We based these assumptions on the other data.

Table 1. Conversion table adapted from Wilkinson et al. (2019)

Inhalation medication group	*kilogram CO2 per canister*
ICS	20.4
LABA	15.6
LABA-ICS, Flutiform	36.5
LABA-ICS, all others	19.6
LABA-LAMA-ICS (assumption)	19.6
SABA	17.2
SABA-ICS (assumption)	19.6
SAMA	14.3

[2] 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:e028763. doi:10.1136/ bmjopen-2018-028763

[3] Jeswani, H. K., & Azapagic, A. (2019). Life cycle environmental impacts of inhalers. *Journal of Cleaner Production, 237*, [117733]. https://doi.org/10.1016/j.jclepro.2019.117733

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Table 2. Conversion table adapted from Yeswani & Azapagic (2019)

Inhalation medication group	*kilogram CO2 per canister*
ICS, brand = Alvesco, ATC = R03BA08	10.946
ICS, all others	14,5
LABA	15.6
LABA-ICS, Flutiform	32.0048
LABA-ICS, all others	14.508
LABA-LAMA-ICS (assumption)	14.5
SABA, brand = Airomir_	7.696
SABA, all others	23.374
SABA-ICS (assumption)	14.5
SAMA	14.17

Calculate the impact of a 70% decrease of pMDI use. In 2020 in the Netherlands 49.6% of inhalation medication DDDs consist of pMDIs. We assume this can safely be lowered to 15%, which is equal to a 70% decrease ((49.6% - 15%)/49.6%). We have two arguments for this assumption:

1) Current Dutch COPD-guidelines[4] state that children younger than 7 years and patients with severe COPD are more dependent on pMDIs. Children cannot yet coordinate their breathing well and need an pMDI and a spacer, and patients with 'severe' COPD have a low inspiratory flow and therefore require the force of a pMDI propellant. We defined 'severe COPD' as COPD requiring at least 42 DDDs of oral corticosteroids per year, which is equal to two treatments of exacerbations. In our data we observed that 13.6% of pMDI DDDs were prescribed for patients who were either younger than 7 years or had severe COPD. If we leave their pMDI DDDs untouched, a replacement of 86.4% would theoretically be possible (100 - 13.6)/100).

[4] Bischoff E, Bouma M, Broekhuizen L, Donkers J, Hallensleben C, De Jong J, Snoeck-Stroband J, In 't Veen JC, Van Vugt S, Wagenaar M. NHG | Nederlands Huisartsen Genootschap (2021) *NHG-richtlijn COPD* [Dutch College of General Practitioners Guideline COPD]. Available: https://richtlijnen.nhg.org/standaarden/COPD. [Accessed 19 Apr 2021].

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

2) In Sweden approximately 10% of inhalation medication consists of pMDIs. [5] If we assume that Sweden and The Netherlands are quite comparable in terms of a variety of social-epidemiological indicators we believe the latter country should be able to lower their percentage of DDDs delivered by pMDIs to 15%.

Step 4: Calculate the financial impact or replacement from pMDI to NPI

Calculate the financial impact with two scenario's:

1) Low-cost scenario
   Calculate the costs of all pMDI medication and spacers in 2020. Add these costs and multiply by the replacement percentage of 70. These are the current costs.
   Divide the pMDI medication into the groups: SABA, LABA, ICS, SAMA, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 70% of pMDI DDDs would be replaced by the low cost NPI in the same group. These are the replacement costs.

2) Average-cost scenario
   Calculate the costs of all pMDI medication and spacers in 2020. Add these costs and multiply by the replacement percentage of 70. These are the current costs.
   Divide the pMDI medication into the groups: SABA, LABA, ICS, SAMA, LABA-ICS and LABA-LAMA-ICS. Within each group calculate the costs if 70% of pMDI DDDs would be replaced by the weighted average cost of NPI of the same group. These are the replacement costs.

[5] Lavorini F, Corrigan CJ, Barnes PJ, Dekhuijzen PR, Levy ML, Pedersen S, Roche N, Vincken W, Crompton GK; Aerosol Drug Management Improvement Team. Retail sales of inhalation devices in European countries: so much for a global policy. Respir Med. 2011 Jul;105(7):1099-103.

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Outcome of steps 1 and 2

Table 3: Inhaler use by diagnosis (nebulizers were excluded, soft mist inhalers were included within DPI).

Type of inhaler	*Patient has diagnosis*	*Number of patients/ users **	*Number of DDDS of inhalation medication*	*pMDIs prescribed for asthma*	*pMDIs prescribed for COPD*
pMDI	n.a.	513,764	65,564,970		
NPI	n.a.	471,340	74,683,448		
pMDI	Asthma	164,684	49,196,500	49,196,500	
NPI	Asthma	123,875	29,019,163		
pMDI	COPD	156,281	54,771,181		54,771,181
NPI	COPD	206,782	70,717,311		
pMDI	Asthma and COPD	21,697	8,584,064	4,292,032	4,292,032
NPI	Asthma and COPD	20,999	6,743,472		
Total			359,280,109	53,488,532	59,063,213

It is clear that pMDI use is not very different between patients with asthma and patients with COPD. It is also clear that primary care diagnoses of asthma and COPD are missing.

Table 4. Inhalation medication in the Netherlands 2020

Inhaler type	Number of patients *	Number of DDDs **
Pressured Metered-dose (pMDI)	856,425	178,116,715
Non-propellant (NPI)	822,996	181,163,394
Nebulizers (excluded in further analysis)	24,178	4,831,798
pMDI and/or NPI (included)	1,429,677	359,280,109
pMDI and/or NPI and/or nebulizers (total group)	1,434,311	364,111,907

* *Patients may use different types of inhalers at the same time*
** *Defined daily dose*

In addition 544544 spacers have been issued to 509650 (pMDI using) patients, so 60% of the pMDI-users received a new, yearly-to-be-replaced, inhaler.

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Table 5. Patient groups not eligible for pMDI to NPI replacement (nebulizers were excluded)

Patient group	*Number of patients*	*Their consumption of pMDI medication (in DDD)*	*Percentage of their pMDI consumption as part of all pMDI consumption*
Severe COPD (COPD and at least 42 DDD prednisone per year)	47,068	19,532,565	11.0%
Younger than 7 years of age	75,948	4,583,947	2.6%
All others	1,311,295	154,000,203	86.5%
		178,116,715	100%

Outcome of step 3

Table 6. Number of canisters per group, calculated with product specifications

Inhalation medication group	*Number of pMDI DDDs*	*Number of pMDI canisters*
ICS	48,206,256	941,550
LABA	12,145,621	278,581
LABA-ICS	56,693,829	1,759,025
LABA-LAMA-ICS	7,066,541	235,406
SABA	38,408,864	1,536,355
SABA-ICS	0	0
SAMA	10,397,516	311,303
Total	172,918,627	5,062,219

The underlying calculations are at product level, and are not shown here.

Table 7. Reduction of CO_2 equivalents due to theoretical 70% exchange of pMDI for NPI

	Using conversion table from Yeswani	*Using conversion table from Wilkinson*
Kilogram CO2 equivalent	85,917,365	94,326,670
70% reduction of pMDI use (in Kilogram CO2 equivalent)	60,142,156	66,028,669

Ten Have P, Van Hal P, Wichers I, Kooistra, J, Hagedoorn P, Brakema EA, Chavannes NH, De Heer, P & Ossebaard HC (2021) Turning green: the impact of changing to more eco-friendly respiratory healthcare. A carbon and cost analysis of Dutch prescription data. Corresponding author: Hans C Ossebaard PhD, National Health Care Institute, P.O. Box 320, 1110 AH, Diemen, The Netherlands. hossebaard@zinl.nl

SUPPLEMENTARY FILE: DATA ANALYSIS PROTOCOL

Outcome of step 4

Table 8. Financial impact of 70% replacement of pMDI to NPI

	DDDs of pMDI, which can be replaced	*Portion of pMDI to be replaced (70%)*	*Low-cost scenario*	*Average-cost scenario*
Volume in DDD	172,918,633	121,043,043	121,043,043	121,043,043
Medication cost	€ 129,856,283	€ 90,899,398	€ 54,419,848	€ 107,245,032
Cost of spacers	€ 18,004,187	€ 12,602,931	€ 0	€ 0
Total cost	€ 147,860,470	€ 103,502,329	€ 54,419,848	€ 107,245,032
Impact of replacement			€ 49,082,481 savings	€ 3,742,703 increased cost

The low-cost scenario would result in €49.1 million annual savings, the average-cost scenario would result in € 3.7 million annual extra expenditure.