SUPPLEMENTAL INFORMATION

Background

Historically, propellants were chlorofluorocarbons, which have an ultra-high global warming potential (GWP) and are ozone-depleting substances. Their phase-out was mandated by the Montreal Protocol in 1987.[1] Following reformulation and transition, current pMDIs use one of two hydrofluoroalkane (HFA) propellants, HFA-134a or HFA-227ea; both propellants are not ozone-depleting but are still greenhouse gases with high or very high-GWP, respectively.[2] With growing concerns over climate change, a strategy to reduce the use of high-GWP hydrofluorocarbon propellants and instead encourage use of low-GWP alternatives was agreed, through adoption of the Kigali Amendment to the Montreal Protocol.[3]

GWP100 values

The values used in the analyses for GWP over 100-year time horizon (GWP100) for the different propellants were taken from the Intergovernmental Panel on Climate Change fifth assessment report (IPCC AR5).[2] After the analyses were performed, a later IPCC AR6 report was released with small changes to the GWPs. However, since these changes were small, and do not alter the overall findings, new analyses were not conducted.

Scenario analysis – additional information

The four scenarios were selected based on new policy recommendations, eg, the ones proposed for the UK, put forward by the House of Commons Environmental Audit Committee in 2018.[4, 5] Suggestions from this report aimed to reduce the climate impact of inhalers, wherever possible.

Scenario 1: Switch from pMDIs to DPI/SMIs

The switch from pMDIs to DPI/SMIs assumed a 1:1 correspondence between products containing the same active drug(s); where this was not possible, an alternative product with the same drug class(es) was assumed.

The transition period of 10 years (2020–2030) for switching from pMDIs to DPI/SMIs was based on the timelines advised in the Kigali amendment to the Montreal Protocol, to reduce the use of hydrofluorocarbons.[3] According to this amendment, developed countries should not exceed the designated hydrofluorocarbon level of consumption over a 12-month period. Consumption is capped at 90% (of the average baseline value) for 2019 to 2023, falling to 15% in 2036.[3] Furthermore, the UK aims to cut gas emissions by two-thirds before 2030.[4]

Scenario 2: Transition to low-GWP propellant

The hydrofluoroalkane (HFA) propellant, HFA-152a, has a substantially reduced GWP of 138 (100-year time horizon).[2]. HFA-152a has a GWP that is 11% and 4% of the value of HFA 134a and HFA-227ea, respectively.[2]

A 6-month period to transition from the old to the new propellant in the market was assumed. At the end of this transition, only HFA-152a pMDIs would be available. It was assumed that use of the new propellant would commence as soon as available in the market, ie, at the start of the transition period.

Scenario 3: Optimisation of asthma maintenance therapy to reduce SABA use

Based on prior evidence, the use of two canisters of SABA per year is considered "target maximal use", with anything exceeding this considered as "higher use". Previous studies [6, 7, 8, 9] provide reference data enabling estimation of the share of higher SABA use as 77% in the UK, 34% in Italy, 67% in France, 60% in Germany, and 67% in Spain. Data also show that higher use differs by disease severity.[6] The recent 2019 Global Initiative for Asthma update no longer recommends treating adolescents and adults with as-needed SABA alone for symptom relief.[10, 11]

Based on the SYGMA studies referenced within the latest revision of GINA guidelines, it was assumed that for all patients overusing SABA, the use of "as needed" ICS/formoterol combination is introduced to replace SABA as reliever and without the need of additional maintenance therapy. Therefore, for each patient overusing SABA, all the SABA consumption is substituted with two ICS/formoterol inhalers per year.[10]

This transition period was determined according to the timelines advised in the Kigali amendment to the Montreal Protocol.[3]

Scenario 4: Inhaler end-of-life treatment

The main source of greenhouse gas emissions during the end-of-life stage of an inhaler (96–99%) is the release of the leftover propellant due to included security doses.

For domestic disposal (treated as non-hazardous waste) and pharmacy disposal (treated as hazardous waste), three treatment processes were identified: landfill, incineration, and incineration with energy recovery. As the share of recycled inhalers is increased, an equal decrease, spread across domestic disposal and return to pharmacy, is assumed (weighted by initial share).

The share of each type of disposal treatment was determined for each reference market and combined with the carbon footprint of each treatment (which included the weight of the waste, ie, of the disposed inhalers). Four different levels of recycling were evaluated: 10%, 30%, 50%, and 100% of inhalers recycled.

Source data used in the study

Data used in this study were internally verified and provided by the sponsor (Chiesi Farmaceutici, Italy) or were retrieved from peer reviewed publications or recognised databases by Aequilibria (Venezia, Italy)

Domestic disposal of pharmaceutical waste

Domestic disposal shares (Eurostat, 2016)

	UK	Italy	France	Germany	Spain
Landfill	42.52%	35.78%	23.08%	0.25%	82.87%
Incineration	16.16%	13.76%	35.74%	0.79%	1.10%
Incineration with energy recovery	41.31%	50.46%	41.18%	98.96%	16.03%

Eurostat Database, 2016, "Domestic Wastes. Treatment of waste by waste category, hazardousness and waste management operations [env_wastrt]". Available at: https://ec.europa.eu/eurostat/data/database

Pharmacy disposal of pharmaceutical waste

Pharmacy disposal shares (Eurostat, 2016)

	UK	Italy	France	Germany	Spain
Landfill	0.00%	0.00%	0.05%	0.00%	0.00%
Incineration	100.00%	67.64%	86.38%	73.09%	75.56%
Incineration with energy recovery	0.00%	32.36%	13.57%	26.91%	24.44%

Eurostat Database, 2016, "Health care and biological wastes. Treatment of waste by waste category, hazardousness and waste management operations". Available at: https://ec.europa.eu/eurostat/data/database

Type of end of life treatment of inhalers in each country

Type of EoL treatment in each country

	UK	Italy	France	Germany	Spain
Domestic disposal	71%	60%	44%	72%	72%
Return to pharmacy	28%	40%	56%	28%	28%
Recycled	0.55%	0%	0%	0%	0%

https://uk.gsk.com/media/920957/2020-ctc-patient-leaflet-downloadable-final.pdf

https://www.pharmaceutical-journal.com/opinion/editorial/breath-of-fresh-air-why-it-is-time-for-a-national-drive-to-recycle-used-inhalers/20206619.article

https://uk.gsk.com/en-gb/responsibility/our-planet/complete-the-cycle/

https://www.fedaiisf.it/farmaci-green-health-come-impiegare-appropriatamente-e-smaltire-correttamente-i-farmaci/

https://www.cyclamed.org/cyclamed/en-chiffres/

Supplemental Table 1. Number of equivalent-months of treatment sold in each market in 2019.

		UK	Italy	France	Germany	Spain
pMDI	ICS	14 296 821	1 361 038	4 474 635	3 046 323	2 036 588
	LABA	473 490	331 096	1 668 914	469 881	105 648
	ICS/LABA	11 312 324	3 149 870	3 163 774	4 899 752	3 063 012
	ICS/LABA/LAMA	904 681	149 327	153 467	463 550	160 081
DPI/ SMI	ICS	425 232	198 643	1 011 771	2 885 461	729 403
	LABA	243 504	626 933	1 157 138	2 598 831	436 948
	ICS/LABA	9 737 303	5 941 986	10 487 965	9 268 992	6 979 534
	LAMA	7 141 215	4 304 075	3 517 636	5 224 707	3 802 077
	LAMA/LABA	2 007 320	924 306	2 196 377	4 814 137	2 680 419
	ICS/LABA/LAMA	964 192	122 144	247 924	368 403	71 393

Total unit sales for each product in 2019 were multiplied by a coefficient representing the number of equivalent-months of treatment contained within each canister of each product: one if the treatment lasted 1 month; 1.67 if the treatment lasted 50 days; two if the treatment lasted 2 months.

DPI dry-powder inhaler, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *pMDI* pressurised metered-dose inhaler, *SMI* soft mist inhaler.

Pernigotti D, *et al. BMJ Open Resp Res* 2021; 8:e001071. doi: 10.1136/bmjresp-2021-001071

Supplemental Table 2. Carbon footprint per month of treatment for each product.

		Molecule	Product	Carbon footprint per month of treatment (kg CO_2e)
pMDI[a]	ICS	Beclometasone	Clenil (Chiesi)	9.9
			Non-Chiesi product average	12.12
		Budesonide	Budiair (Chiesi)	12.12
		Ciclesonide	Alvesco (AstraZeneca)	12.12
		Fluticasone	Non-Chiesi product average	12.12
	LABA	Formoterol	Atimos (Chiesi)	7.5
			Non-Chiesi product average	7.5
		Salmeterol	Non-Chiesi product average	15
	ICS/LABA	Beclometasone/Formoterol	Fostair/Foster/Inuver/Innovair/Formodual (Chiesi)	12.6
		Budesonide/Formoterol	Symbicort (AstraZeneca)	36.5
		Fluticasone/Formoterol	Flutiform/Abriff (Mundipharma)	36.5
		Fluticasone/Salmeterol	Non-Chiesi product average	19.65
	ICS/LABA/ LAMA	Beclometasone/Formoterol/Glycopyrronium	Trimbow (Chiesi)	14.28
	SABA[b]	Salbutamol	Non-Chiesi product average	28.0
DPI	ICS	Beclometasone	Non-Chiesi product average	0.75
		Budesonide	Non-Chiesi product average	0.75
		Fluticasone propionate	Non-Chiesi product average	1.25
		Mometasone	Asmanex (Merck)	1.25
	LABA	Formoterol	Non-Chiesi product average	1.25

		Indacaterol	Onbrez (Novartis)	0.75
		Salmeterol	Non-Chiesi product average	1.25
	ICS/LABA	Beclometasone/Formoterol	Fostair/Foster/Inuver/Innovair/Formodual (Chiesi)	0.92
		Budesonide/Formoterol	Non-Chiesi product average	1.0
		Fluticasone furoate/Vilanterol	Relvar/Revinty (GlaxoSmithKline)	0.75
		Fluticasone propionate/Salmeterol	Non-Chiesi product average	1.25
	LAMA	Aclidinium bromide	Elkira/Bretaris (AstraZeneca)	1.25
		Glycopyrronium	Seebri/Tovanor (Novartis)	0.75
		Tiotropium bromide	Non-Chiesi product average	0.75
		Umeclidinium bromide	Incruse/Rolufta (GlaxoSmithKline)	0.75
	LAMA/LABA	Aclidinium bromide/Formoterol	Duaklir/Brimica (AstraZeneca)	1.25
		Glycopyrronium/Indacaterol	Ultibro/Xoterna (Novartis)	0.75
		Umeclidinium bromide/Vilanterol	Anoro/Laventair (GlaxoSmithKline)	0.75
	ICS/LABA/ LAMA	Fluticasone furoate/Umeclidinium bromide/Vilanterol	Non-Chiesi product average	0.75
	SABA[b]	Salbutamol	Non-Chiesi product average	0.6
SMI	LABA	Olodaterol	Striverdi (Boehringer Ingelheim)	0.78
	LAMA	Tiotropium bromide	Spiriva (Boehringer Ingelheim)	0.78
	LAMA/LABA	Tiotropium bromide/Olodaterol	Spiolto (Boehringer Ingelheim)	0.78

The derived monthly carbon footprint for each product is based on the number of actuations per canister (excluding security doses) and the Carbon Footprint of Product (CFP) per individual actuation.

CO_2e carbon dioxide equivalent, *DPI* dry-powder inhaler, *HFA* hydrofluoroalkane, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *pMDI* pressurised metered-dose inhaler, *SABA* short-acting β_2-agonist, *SMI* soft mist inhaler.

Supplementary material

[a]All pMDI products use HFA-134a as the propellant, except for two ICS/LABA products (Symbicort and Flutiform/Abriff), which both use HFA-227ea as the propellant.

[b]For SABA products, the stated carbon footprint refers to that of the canister rather than monthly use.

Reference sources for this information:

1. Chiesi Farmaceutici products: Panigone S, Sandri F, Ferri R, Volpato A, Nudo E, Nicolini G. Environmental impact of inhalers for respiratory diseases: decreasing the carbon footprint while preserving patient-tailored treatment. *BMJ Open Respir Res* 2020 r;7:e000571. doi: 10.1136/bmjresp-2020-000571.
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    b. GlaxoSmithKline PLC Product carbon footprint certification summary report. Available: https://networks.sustainablehealthcare.org.uk/sites/default/files/media/GSK%20Carbon%20Trust%20Certification%202014.pdf [Accessed 25 October 2021].
3. Boehringer Ingelheim products: 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;36:2487–92. doi: 10.1007/s12325-019-01028-y.
4. For allother products, the average indicated in the following publication was used: 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.

Supplementary material

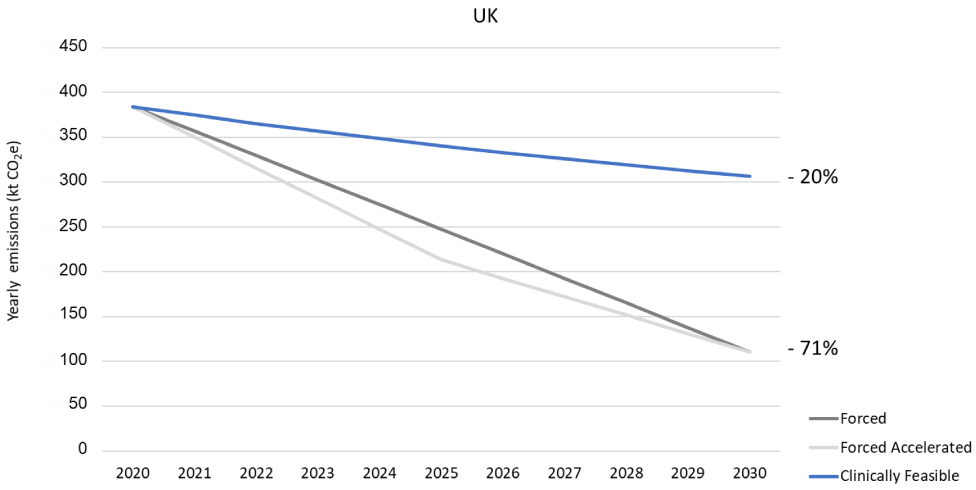
Supplemental Table 3. pMDI to DPI/SMI active drug correspondence.

Class	**pMDI**	**DPI/SMI**
LABA	Formoterol	Formoterol
LABA	Salmeterol	Salmeterol
ICS/LABA	Beclometasone/Formoterol	Beclometasone/Formoterol
ICS/LABA	Budesonide/Formoterol	Budesonide/Formoterol
ICS/LABA	Fluticasone/Salmeterol	Fluticasone/Salmeterol
ICS/LABA	Fluticasone/Formoterol	Beclometasone/Formoterol
ICS/LABA/LAMA	Beclometasone/Formoterol/ Glycopyrronium	Fluticasone furoate/Umeclidinium bromide/Vilanterol
ICS	Fluticasone	Fluticasone
ICS	Ciclesonide	Budesonide
ICS	Beclometasone	Beclometasone
ICS	Budesonide	Budesonide

DPI dry-powder inhaler, *ICS* inhaled corticosteroid, *LABA* long-acting β_2-agonist, *LAMA* long-acting muscarinic antagonist, *pMDI* pressurised metered-dose inhaler, *SMI* soft mist inhaler.

Supplemental Figure 1. Total yearly CO_2e emissions reduction, by 2030, in the three sub-scenarios of switch from pMDIs to DPI/SMIs (excluding SABA inhalers). a) UK, b) Italy, c) France, d) Germany and e) Spain.

a)



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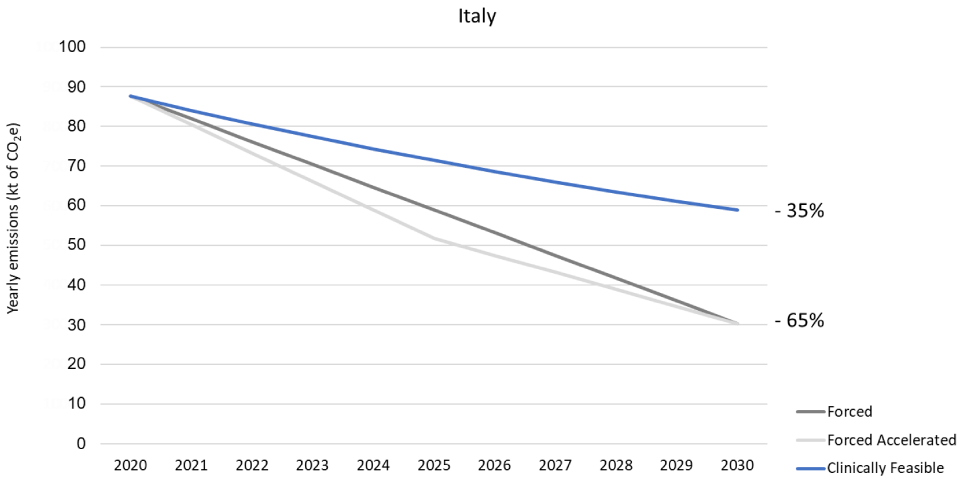

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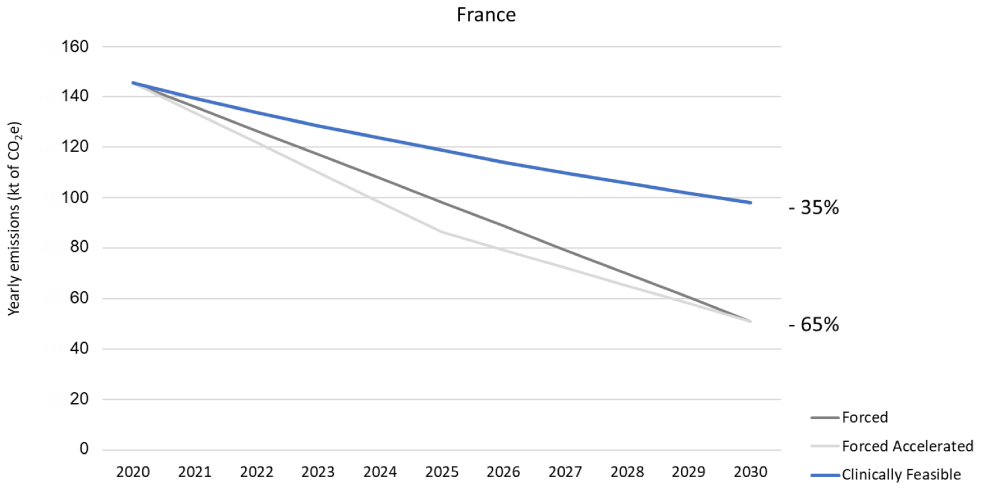

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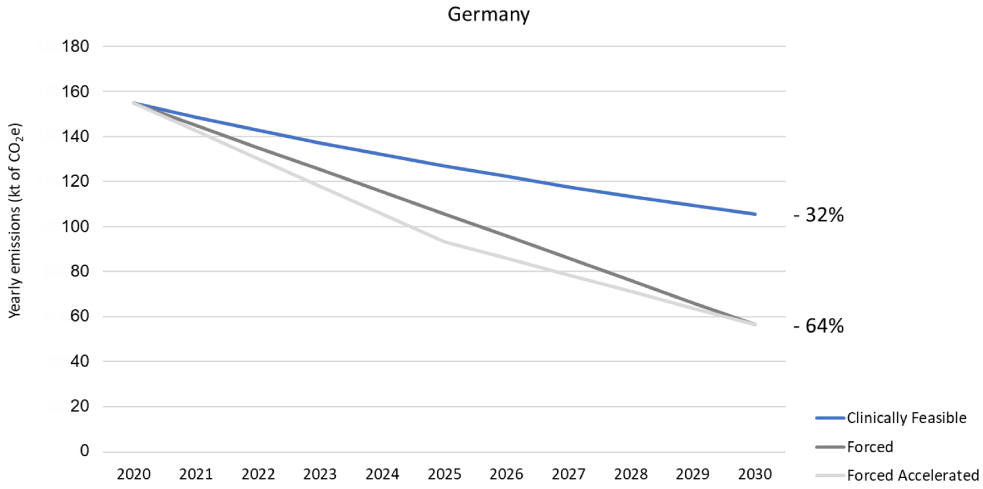

Supplementary material

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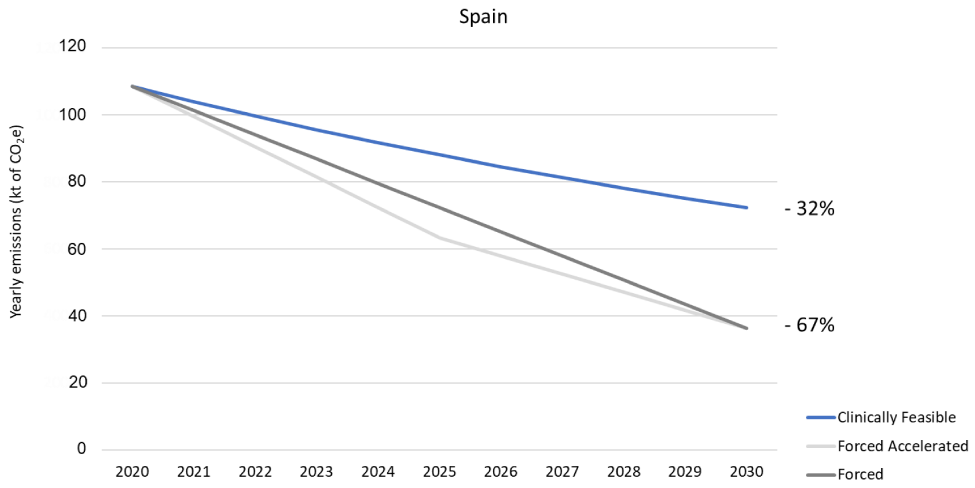
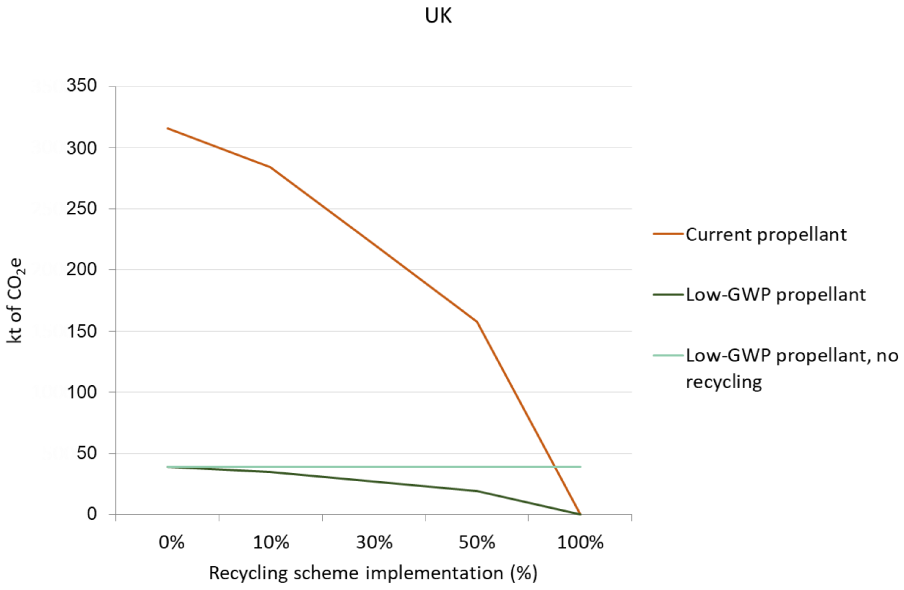


Supplementary material

Supplemental Figure 2. End-of-life CO_2e emissions reduction including both pMDI and DPI/SMI products, for different levels of recycling scheme implementation for the a) UK, b) Italy, c) France, d) Germany and e) Spain reference markets.

Substantial reductions in inhaler end-of-life emissions each year increase with increasing levels of inhaler recycling (10%, 30%, 50%, and 100% of inhalers recycled). End-of-life greenhouse gas emissions include the release of the leftover propellant due to security doses and emissions due to device disposal treatment (landfill, incineration, incineration with energy recovery). *GWP* global warming potential (100-year time horizon), *pMDI* pressurised metered-dose inhaler.

a)



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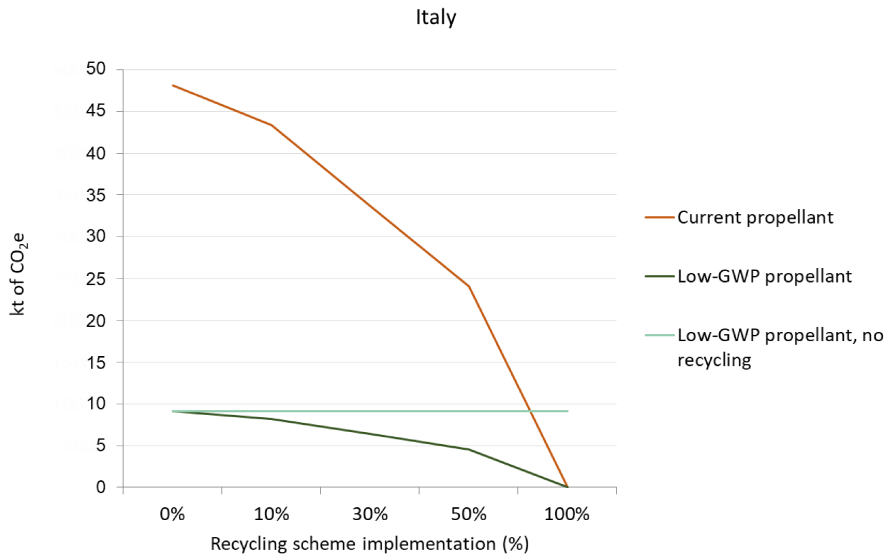

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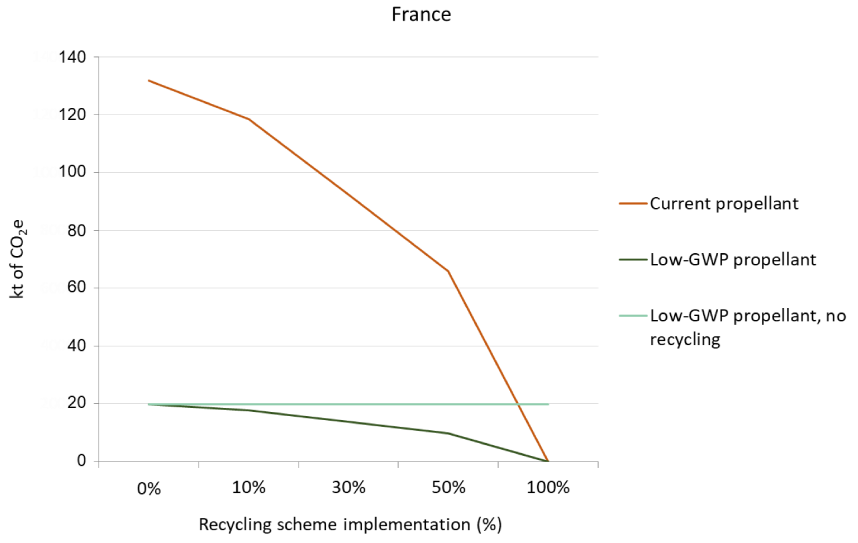

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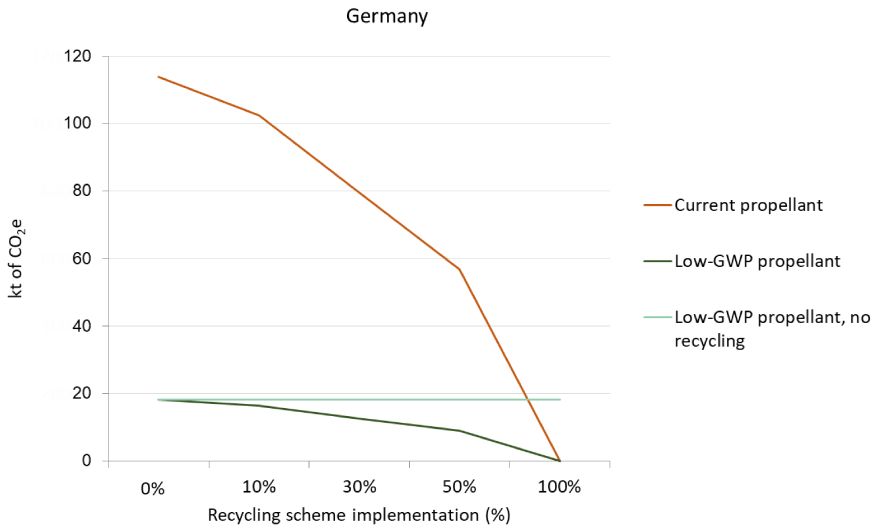

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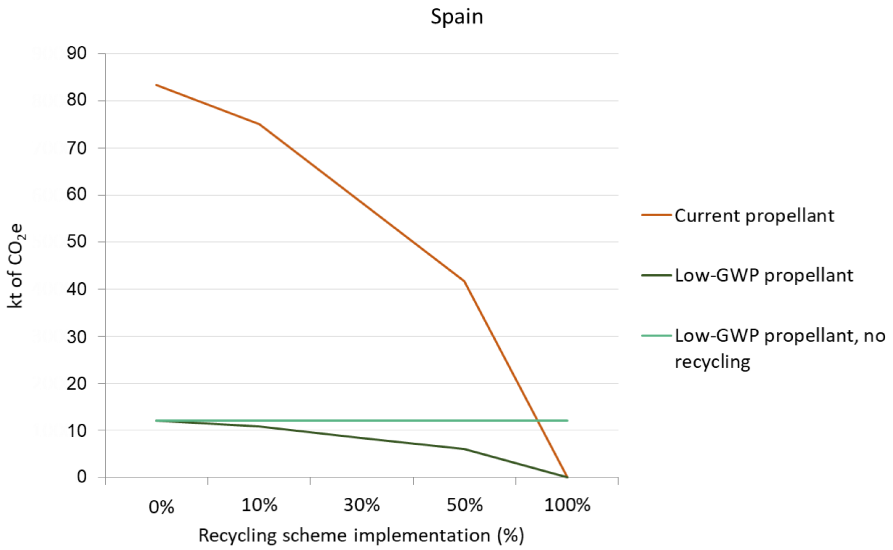
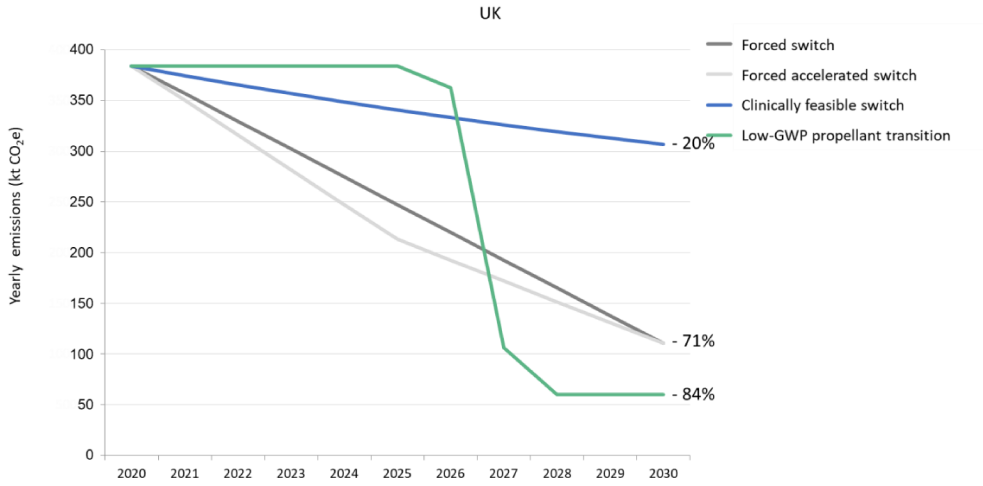


Supplementary material

Supplemental Figure 3. Comparison of differences in the yearly emissions reduction trends considering switch from pMDIs to DPI/SMIs (three sub-scenarios) and low-GWP propellant transition (whole market excluding SABA inhalers), for a) UK, b) Italy, c) France, d) Germany and e) Spain.

a)



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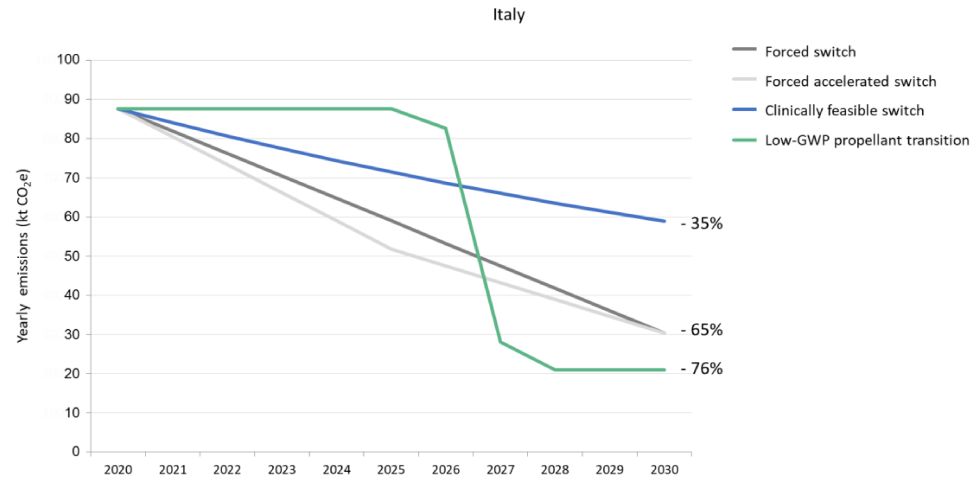

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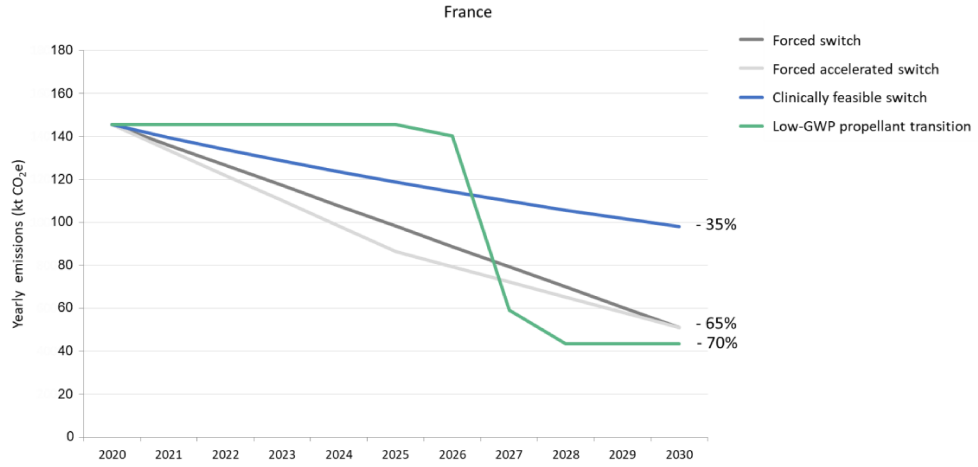

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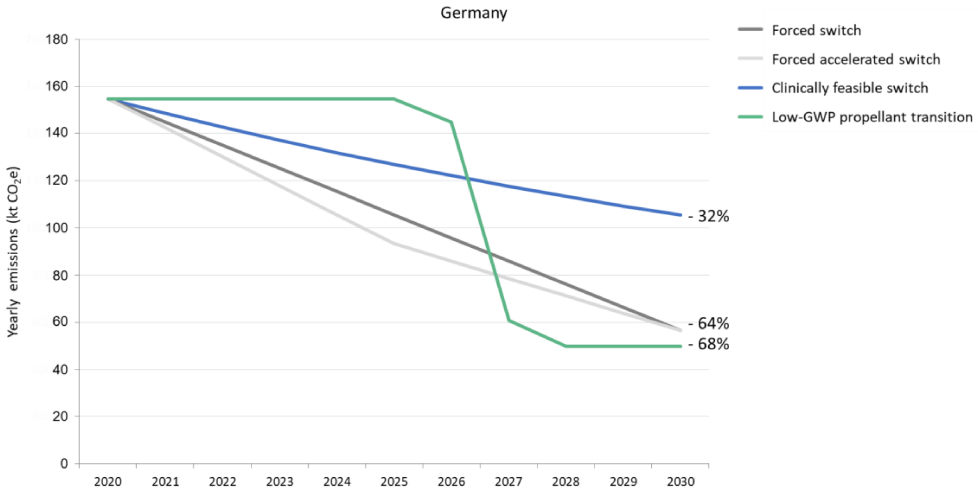

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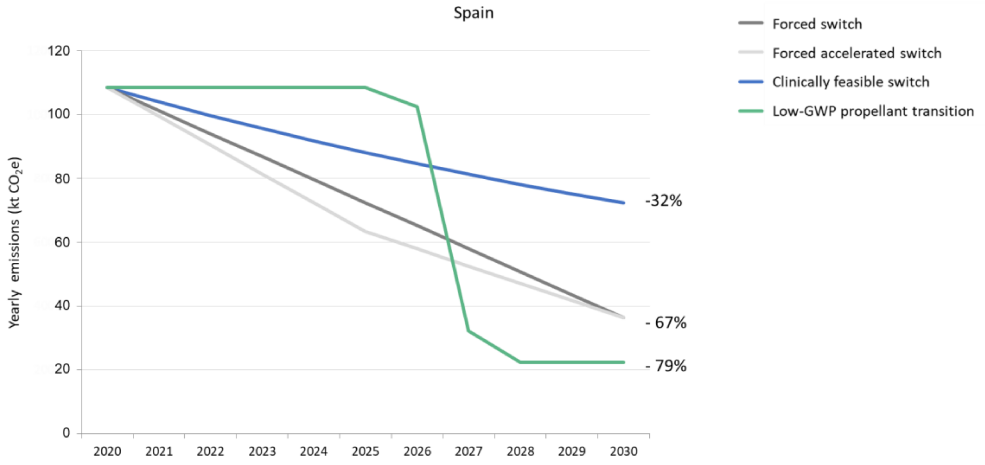

Supplementary material

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11. Janson C, Henderson R, Löfdahl M, et al. Carbon footprint impact of the choice of inhalers for asthma and COPD. *Thorax* 2020;75:82–4. doi: 10.1136/thoraxjnl-2019-213744.

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