WEB-APPENDICES

e-Figure 1. Components of life cycle assessment from cradle to grave
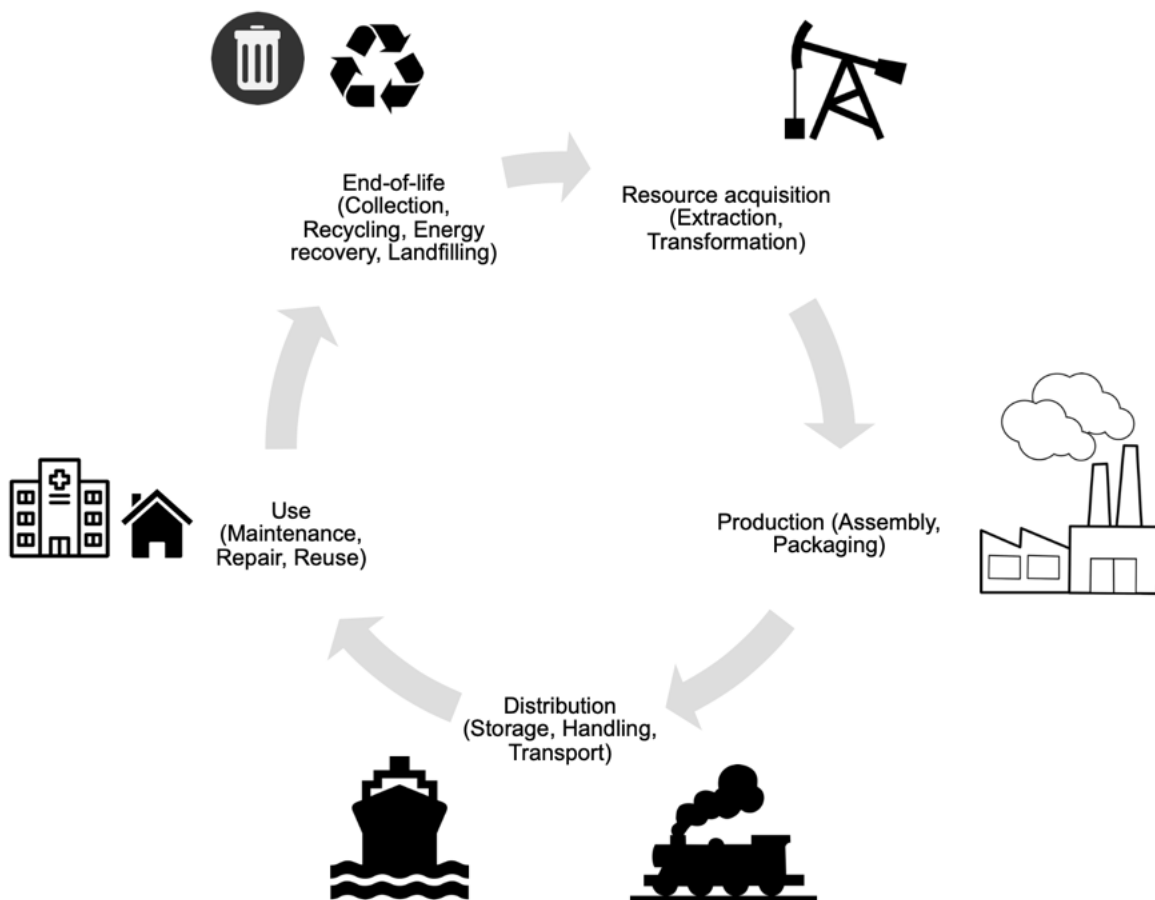

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e-Appendix 1. Description of the methods for identifying gas composition in the metered-dose inhaler canister

The identity of the major volatile components of the mixture within salbutamol canisters was ascertained by multinuclear nuclear magnetic resonance (NMR) spectroscopy and gas-phase infrared (IR) spectroscopy. Volatile but condensable (most volatiles excluding extremes like N_2, O_2, etc.) substances were collected using a setup inspired by ref[1] consisting of an anesthesia bag, into which the salbutamol canister and pump assembly was placed, connected to a high-vacuum line with calibrated volumes equipped with a train of U-traps for fractional condensations. Such a setup allowed for the exclusion of moisture from the environment. Ideal gas behavior was used as an approximation and the ideal gas law was used to determine the amount of materials collected in the gas phase. This approximation is widely useable, especially with species well above their boiling point, and typically gives results well within 95 % accuracy when compared with weighing with an analytical balance.

^1H, ^{19}F and ^{13}C NMR supported by MS indicated that the mixture contained CF_3CFH_2 as the "HFA" propellant.

A canister of GSK brand salbutamol was weighed before (28.7140 g) and after (11.4611 g) being emptied by 200-300 actuations of the pump (17.2582 g of material expelled) The last portion, consisting mostly of gas-phase material, was particularly difficult to extract. We attempted to disassemble the canister by essentially ripping the top apart while cooling the canister to -196 °C (Caution! This operation is dangerous and should only be attempted with proper safety equipment and gas-phase handling techniques). The open canister was quickly placed in a vacuum vessel and attached to high-vacuum line. The volatiles were then collected (empty canister + disassembled parts : 10.9986 g) and approx. 0.3 mmol of material were collected (*maximum 31 mg if composed of CF_3CH_2F*), yielding an estimated total mass of volatile components (excluding the non-volatile salbutamol) of between 17.26 g and 17.7 g. This is in agreement with ref[1], which found *ca* 17.32 g of propellant (likely excluding the gas-phase remainder in the canister).

The composition of the mixture was assumed to be uniform throughout actuations because of the design of the pump, which shoots out the suspension (comprising the liquid propellant, solid salbutamol and other potential formulation ingredients) that vaporizes upon exiting the canister. A sample consisting of the 15 first actuations (1.1204 g weight loss) of a new salbutamol canister (GSK brand) was collected by condensation at -196 °C (1.085 g total based on ideal gas law). Moisture (most likely adventitiously condensed along the propellant during manufacture) could be visually observed in the process in the form of a white, high-melting point solid condensed in the traps. This solid mixture was then fractionally condensed through U-traps at -96 °C, -130 °C and -196 °C under a dynamic vacuum. Approximately (80 µmol, 8 mg)) out of the total volatile components were separated and identified by ^1H NMR spectroscopy and vibrational spectroscopy as water. The rest of the major volatile components were confirmed to be tetrafluoroethane with possible traces of moisture (1.07 g based on ideal gas law). The composition was therefore found to be in agreement with the literature provided with the pump, which lists tetrafluoroethane as the only non-medicinal ingredient.

The literature[1] indicates the use of ethanol in salbutamol pumps. Indeed, a sample of Teva brand salbutamol was found to contain ethanol, as indicated by ^1H NMR spectroscopy. ^1H NMR relative signal integrations, which are a crude approximation for the true composition, suggest a proportion of at most 5 mol% ethanol (2 w/w%). Similarly, semi-quantitative MS

data also suggests a concentration of *ca* 5 mol% of ethanol. These results are in qualitative agreement with ref[1] (1 w/w % ethanol). Despite our best efforts, no ethanol was detected in samples of the GSK brand salbutamol, in agreement with its listed non-medicinal ingredients, which omit ethanol. CO_2 (most likely adventitiously incorporated during the manufacture) was also identified by ^{13}C spectroscopy in samples of the Teva brand salbutamol.

[1] W. F. S. Sellers, *Allergy, Asthma & Clinical Immunology* **2017**, *13*, 30.

e-Figure 2. CO_2 equivalent emissions by Emergency Department treatment of asthma with salbutamol, calculated using the IPCC2021 GWP100 method
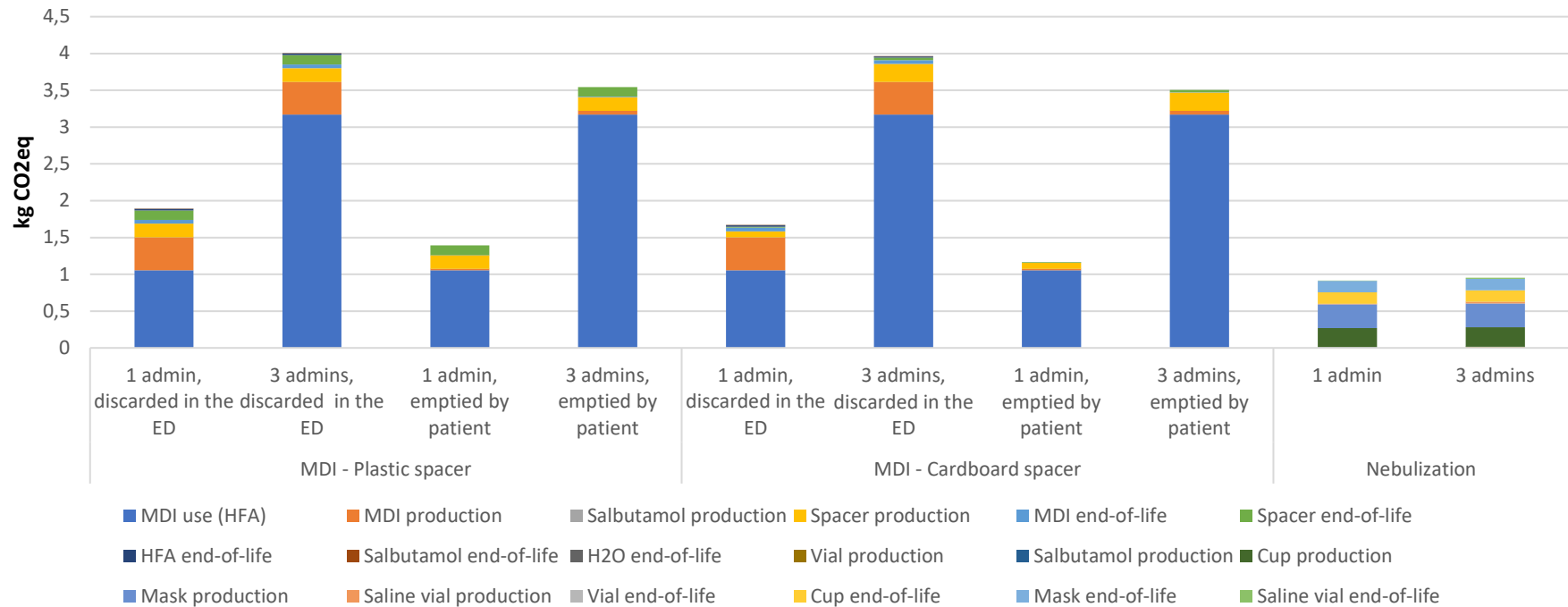
IPCC2021 GWP100: Intergovernmental Panel on Climate Change 2021 Global Warming Potential over a 100-year period
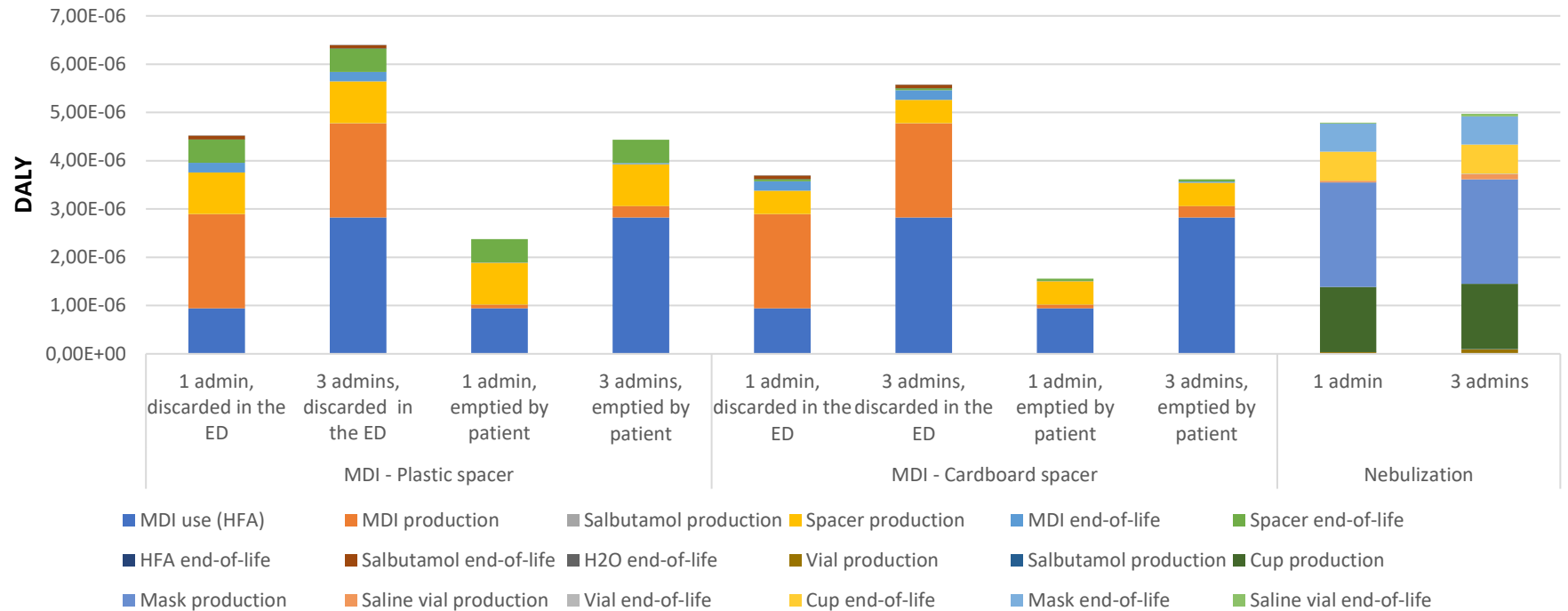CO_2eq: CO2 equivalent emissions
Admin: Administration
ED: Emergency Department
MDI: Metered-dose inhaler
HFA: Hydrofluoroalkane

e-Figure 3. Disability-adjusted life-year loss attributable to the environmental impact of different modes of salbutamol administration in the Emergency Department
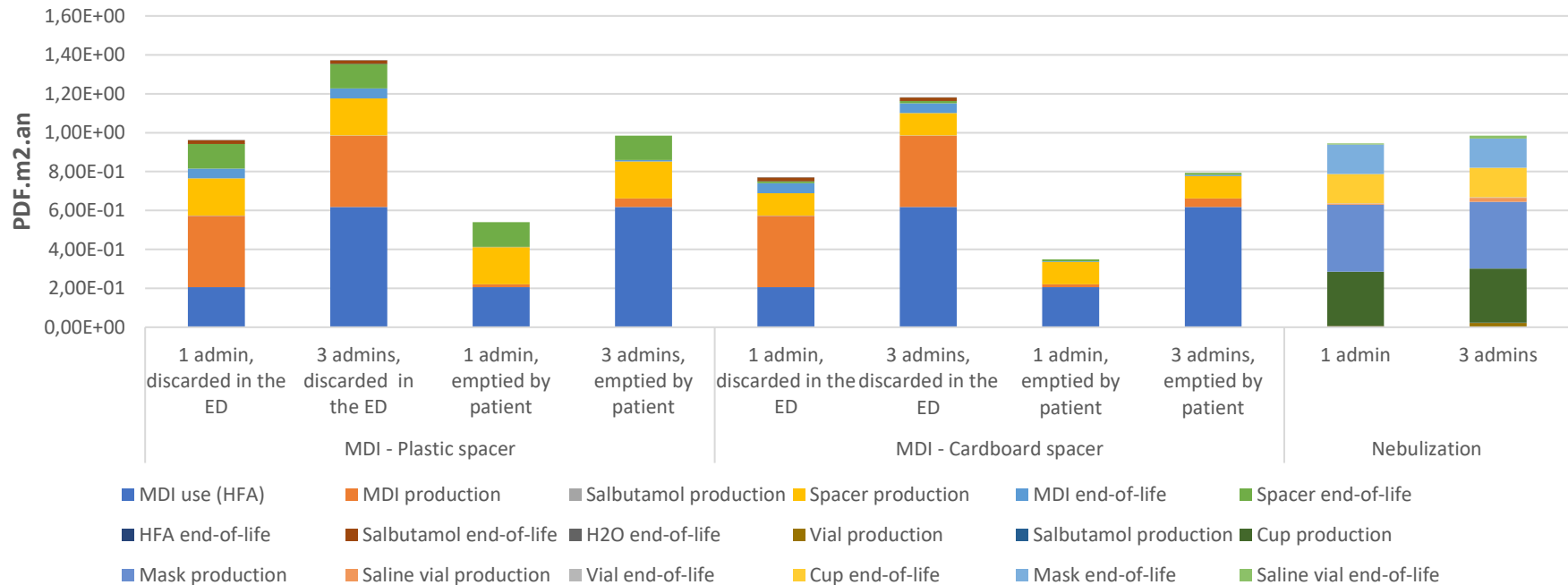
DALY: Disability-Adjusted Life Year
MDI: Metered-dose inhaler
HFA: Hydrofluoroalkane

e-Figure 4. Potential loss of biodiversity attributable to different modes of salbutamol administration in the Emergency Department
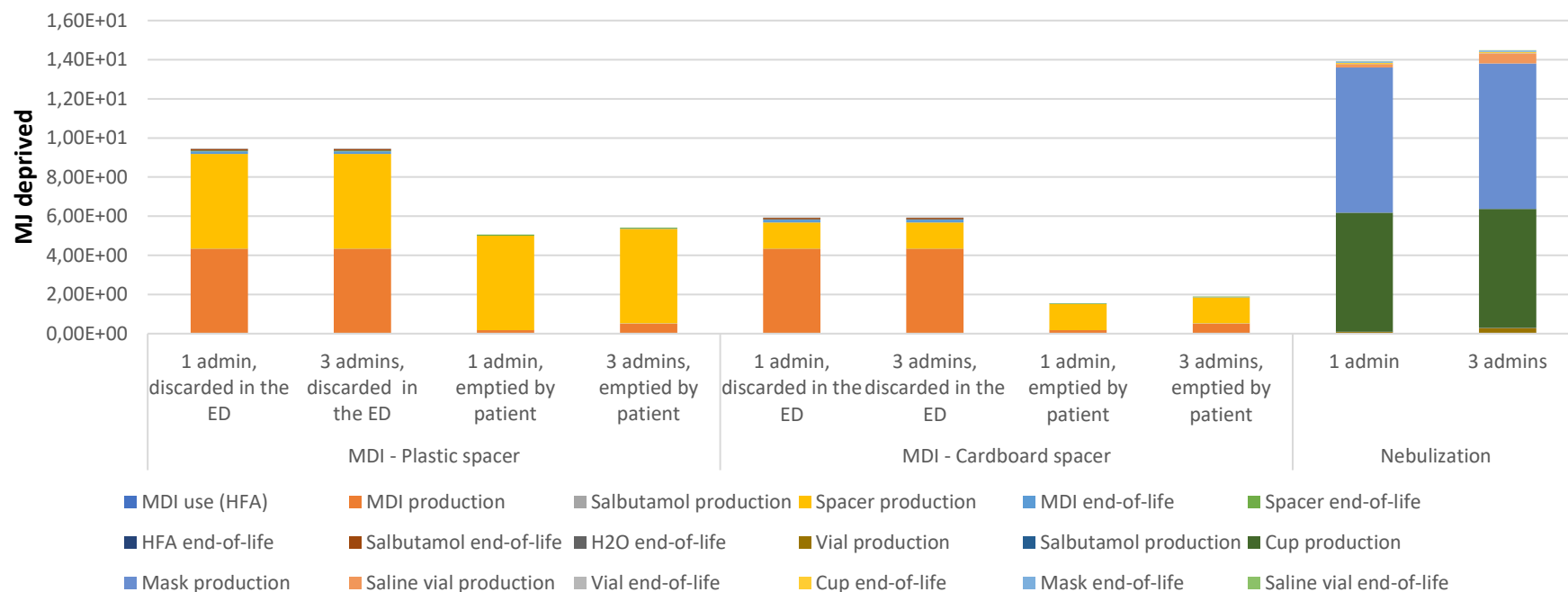
PDF.m^2.year: Potential Loss of Biodiversity per square meter per year
MDI: Metered-dose inhaler
HFA: Hydrofluoroalkane

e-Figure 5. Fossil energy resources use attributable to different modes of salbutamol administration in the Emergency Department

MDI: Metered-dose inhaler
HFA: Hydrofluoroalkane
MJ: Megajoules

e-Table 1. Environmental impacts of Salbutamol administration modes for 1 and 3 administrations in the emergency department when metered-dose inhalers and spacers are left for patient's use at home

Number of times administered	Mode of administration	Climate change (kg CO_2 eq)		Human health (DALY)		Ecosystem quality (PDF·m²·year)		Use of fossil resources (Megajoules deprived)	
		Point estimate*	Monte Carlo** Median (IQR)	Point estimate X 10^{-6}	Monte Carlo Median (IQR) X 10^{-6}	Point estimate	Monte Carlo Median (IQR)	Point estimate	Monte Carlo Median (IQR)
1	MDI/plastic spacer	1.39	1.42 (1.29; 1.54)	2.3	0.7 (-25.7; 25.2)	0.54	0.55 (0.43; 0.67)	5.06	5.17 (5.00; 5.37)
	MDI/cardboard spacer	1.17	1.18 (1.06; 1.30)	1.4	-3.8 (-57.3; 51.3)	0.34	0.36 (0.22; 0.50)	1.54	1.61 (1.54; 1.68)
	Nebulization	0.95	1.10 (1.06; 1.14)	3.9	13.0 (-191.2; 185.5)	0.97	1.12 (0.33; 1.94)	14.00	16.77 (16.08; 17.53)
3	MDI/plastic spacer	3.54	3.57 (3.23; 3.90)	4.3	6.1 (-19.9; 34.8)	0.98	1.00 (0.86; 1.15)	5.42	5.54 (5.34; 5.73)
	MDI/cardboard spacer	3.51	3.53 (3.16; 3.95)	4.3	18.7 (-131.3; 177.5)	1.03	1.08 (0.61; 1.47)	4.61	4.82 (4.60; 5.06)
	Nebulization	0.99	1.13 (1.10; 1.18)	4.0	2.7 (-186.0; 206.1)	1.01	1.25 (0.36; 2.10)	14.60	17.38 (16.63; 18.13)