Marquette University
e-Publications@Marquette

Civil and Environmental Engineering Faculty Research and Publications

Civil and Environmental Engineering, Department of

9-26-2017

A Comparative Life Cycle Assessment between a Metered Dose Inhaler and Electric Nebulizer

Brandon Goulet
Marquette University

Lars E. Olson
Marquette University, lars.olson@marquette.edu

Brooke K. Mayer
Marquette University, Brooke.Mayer@marquette.edu

Article

A Comparative Life Cycle Assessment between a Metered Dose Inhaler and Electric Nebulizer

Brandon Goulet [1], Lars Olson [1] and Brooke K. Mayer [2],*

[1] Department of Biomedical Engineering, Marquette University and Medical College of Wisconsin, Milwaukee, WI 53233, USA; Brandon.Goulet@marquette.edu (B.G.); Lars.Olson@marquette.edu (L.O.)

[2] Department of Civil, Construction and Environmental Engineering, Marquette University, Milwaukee, WI 53233, USA

* Correspondence: Brooke.Mayer@marquette.edu; Tel.: +1-414-288-2161

Abstract: Life cycle assessment (LCA) evaluates the environmental impact of a product based on the materials and processes used to manufacture the item as well as the item's use and disposal. The objective of this LCA was to evaluate and compare the environmental impact of a metered dose inhaler, specifically the Proventil® HFA inhaler (Merk & Co., Inc., Kenilworth, NJ, USA), and an electric nebulizer, specifically the DeVilbiss Pulmo-Aide® nebulizer (DeVilbiss, Port Washington, NY, USA). GaBi LCA software was used to model the global warming potential (GWP) of each product by using substantiated data and well-justified assumptions for the components, manufacturing, assembly, and use of both devices. The functional unit used to model each device was one dose of the active drug, albuterol sulfate. The inhaler's GWP, 0.0972 kg CO_2-eq, was greater than the nebulizer's even when uncertain parameters were varied $\pm 100\times$. During the use phase ofa the inhaler, which accounted for approximately 96% of the inhaler's total GWP, HFA 134a is used as a propellant to deliver the drug. The total GWP for the electric nebulizer was 0.0294 kg CO_2-eq assuming that the mouthpiece was cleaned in a dishwasher, while it was 0.0477 kg CO_2-eq when the nebulizer mouthpiece was hand washed between uses. The GWP breakeven scenario between dishwashing and hand washing occurred when the mouthpiece accounted for 10% of the dishwasher load.

Keywords: life cycle assessment (LCA); metered dose inhaler (MDI); nebulizer; chronic obstructive pulmonary disease (COPD); global warming potential (GWP); carbon dioxide (CO_2)

1. Introduction

According to the World Health Organization (WHO), "Climate change is the greatest threat to global public health in the 21st century" [1]. Increasingly greater emphasis has been accorded to this issue in recent years. At the same time, the inverse relationship is also attracting attention: ironically, approximately 10% of global greenhouse gas (GHG) emissions are generated by the healthcare sector alone (8% of total GHG emissions in the U.S.) [2–4]. Yet, the environmental costs of devices, procedures, and facilities in the healthcare sector are often overlooked in spite of significant local, national, and global impacts, including energy and material consumption and emissions that adversely impact environmental and human health [5]. Accordingly, there is significant opportunity for systemic improvements leading to reductions in health-related environmental impacts. In particular, routine inclusion of life cycle criteria is needed as part of device selection to account for total negative healthcare-associated impacts rather than impacts at a single point in time, e.g., during device use [6]. Unfortunately, limited research is currently available describing the environmental costs associated with the healthcare system [5]. Thus, before improvements can be implemented in the healthcare sector, it is imperative to develop a deeper understanding of the associated environmental impacts. One tool that, while still relatively rare, is being increasingly utilized is life cycle assessment.

Life cycle assessment (LCA) provides a quantitative, systematic approach for determining the environmental costs of a product or system over its life cycle, including raw material extraction, production, transportation and distribution, use, and final disposal. This approach can provide a complete "cradle-to-grave" (tracking impacts from extraction to disposal) or "cradle-to-cradle" (tracking impacts from extraction to recycling for reuse) assessment, or can be used to focus on individual phases of the life cycle. LCA is now a common tool to evaluate technologies and systems from an environmental impact standpoint and is being increasingly used to guide design, manufacturing, and logistics. The International Organization for Standardization has published an LCA standard, ISO 14040 [7], which establishes LCA principles and framework.

The specific objective of this study was to evaluate the environmental impacts of systems designed to deliver inhaled medication for treatment of chronic obstructive pulmonary disease (COPD) using LCA. Globally, COPD is the third leading cause of death, with disproportionate effects in developing regions with unreliable electricity [8–10]. COPD also accounts for billions in annual economic losses due to lost workdays [11]. Thus, it is critical that effective and affordable COPD treatments are available to people around the world. It is also imperative to consider the environmental impacts of these treatments, which have yet to be evaluated. In the U.S. and other developed countries, portable metered dose inhalers are most commonly used to treat COPD, while electric nebulizers are most often used in a home or medical facility. Thus, a comparative LCA of an inhaler and nebulizer system was performed in this study. This research is the only known LCA comparing inhalers and nebulizers. It will help to inform COPD treatment device design improvements, and can contribute to calculations of carbon market offsets of COPD treatment devices.

2. Materials and Methods

2.1. Goal and Scope Definition

The purpose of this study was to perform a comparative LCA to evaluate the cradle-to-use phase global warming potential (GWP) of a metered dose inhaler, specifically the Proventil® HFA inhaler, relative to an electric nebulizer, specifically the DeVilbiss Pulmo-Aide® nebulizer (both are pictured in Figure S1 in the Supplementary Data). Both of the devices are used for the treatment of COPD via delivery of the inhalation aerosol drug albuterol sulfate.

The frequency of administration of bronchial dilation drugs (e.g., albuterol sulfate) to a patient varies between the inhaler and nebulizer methods of delivery based on the severity of asthma and the concentration of the drug that is delivered. Thus, to compare the environmental impacts of the inhaler and nebulizer, the functional unit in this study was defined as one dose of albuterol sulfate. A single inhaler can be used to supply 100 doses (2 puffs per dose). The nebulizer was modeled as being able to administer 2000 doses assuming 2–4 treatments per week and a 10 year average lifespan of the compressor [12].

An inventory analysis of the manufacturing processes and materials used to produce the two drug delivery devices was conducted, and the inventories were then modeled using GaBi Product Sustainability software (v. 6) to calculate the products' environmental impact quantified as GWP from cradle through use phase. Transportation and packaging were excluded from the analysis based on preliminary results, which demonstrated that they played insignificant roles in GWP impacts. When possible, pre-defined manufacturing processes included in the GaBi software were used to model the devices since these processes are typically well documented and vetted in terms of material and energy flows. Default process selections used U.S. data, while European process data was used when U.S. data was unavailable.

For consistency, the "US Electricity grid mix PE" GaBi process was used to model all of the electricity inputs. This electricity mix includes the U.S. national average mix of 0.4% geothermal, 0.3% wind, 6.4% hydro, 1.7% waste and biomass, 20% nuclear, 50.7% coal, 2.5% heavy fuel oil, and 20% natural and blast furnace gas energy sources.

2.2. Inventory Analysis: Metered Dose Inhaler

For each drug delivery device, the inventory was prepared by disassembling the device and determining the mass and major composition of each component, as shown for the metered dose inhaler in Table 1. The Proventil® HFA inhaler can be categorized into six major components: the active substance, propellant, surfactant, metering valve, actuator, and canister [13]. The following sections describe the assumptions for the manufacture and assembly of each component used to model the device using manufacturing processes available in the GaBi Professional + Extension XVII database (as shown in the inventory flow diagram in Figure S2 in the Supplementary Data). An inhaler assembly energy input of 1 MJ (0.001 MJ/dose) was estimated based on other manufacturing processes built into the GaBi database.

Table 1. Components of the metered dose inhaler (MDI) including mass (total of 23.4 g), composition, and manufacturing process used in the GaBi life cycle assessment (LCA) model.

Major Components of the MDI	Mass (g)	Composition	GaBi Model Manufacturing Process
Active substance	0.02	Albuterol Sulfate	N/A [1]
Propellant	6.68	HFA-134a	N/A [1]
Surfactant	0.002	Oleic acid and ethanol	N/A [2]
Metering Valve			
Ferrule	1.10	Aluminum	Stamping and Bending
Ferrule Gasket	0.13	High Density Polyethylene (HDPE)	Plastic Injection Molding
Valve Stem	0.30	Stainless Steel	Deep Drawing
Compression Spring	0.09	Steel Wire	Auto Coiler
Tank	0.26	Stainless Steel	Stamping and Bending
Bottle Emptier	0.39	Stainless Steel	Stamping and Bending
Diaphragm	0.07	Nitrile Rubber	Plastic Injection Molding
Tank Seal	<0.01	Nitrile Rubber	N/A [2]
Actuator			
Actuator	8.62	Polypropylene	Plastic Injection Molding
Actuator Cap	1.20	Polypropylene	Plastic Injection Molding
Canister	4.56	Aluminum	Deep Drawing

[1] Not applicable (N/A) as the manufacturing process was modeled as directly combining the materials to output the component using 1 MJ assembly energy input/device; [2] Not applicable (N/A) as this component was excluded from the model due to negligible mass.

2.2.1. Active Substance

The active bronchodilator substance is albuterol sulfate, $(C_{13}H_{21}NO_3)_2 \cdot H_2SO_4$ (also known as salbutamol sulfate, the WHO recommended name). Albuterol sulfate makes up 0.3% of the net weight of the drug [14]. Detailed information about albuterol sulfate and its production is not publicly available. However, since the functional unit in this analysis was a single dose of the drug, an exact representation of the albuterol sulfate itself was not necessary in this comparative LCA since both devices use albuterol sulfate, and the device impacts were normalized to the functional unit of a single dose. Accordingly, a new GaBi process was developed to represent the active substance. A conservative placeholder, chlorodifluoromethane (CHF_2Cl, also known as HCFC-22 or R22), was used to model the active ingredient. HCFC-22 is commonly used as a propellant and is characterized by a high GWP (up to 1700× that of CO_2 [15]); as such, it was anticipated to have greater negative GWP impacts than albuterol sulfate. If the GWP impacts of HCFC-22 were shown to be negligible in the model in comparison to other components, then negligible impacts from albuterol sulfate could also be assumed.

Microionizers using compressed air are used to convert the active drug into an ultra-fine powder [13], so for production of the active substance, a compressed air manufacturing process was used in the GaBi model.

2.2.2. Propellant

The inhaler relies on the propellant to forcefully deliver an aerosolized cloud of the drug (1% albuterol sulfate in saline solution combined with surfactant) to the user. The propellant in Proventil® HFA is hydrofluoroalkane-134a (HFA-134a, or 1,1,1,2-tetrafluoroethane, $C_2H_2F_4$), which represents 99.7% of the net weight of the drug formulation [14]. Production of the propellant was modeled in GaBi as a reaction between hydrogen fluoride (HF) and trichloroethylene (C_2HCl_3) in a closed system [16]:

$$4HF + C_2HCl_3 \rightarrow CH_2FCF_3 + 3HCl$$
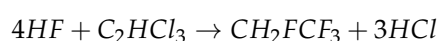
Based on stoichiometry, the chemical reaction to yield 1 kg of HFA-134a requires 0.784 kg of HF and 0.969 kg of C_2HCl_3. When the reactants are in vapor form, the temperature at which the reaction occurs is 380 °C; assuming room temperature initially, this would require 495 kJ of thermal energy input. The reaction also produces 2.14 kg of HCl, which was modeled as being recoverable for reuse for other purposes.

2.2.3. Surfactant

The surfactant allows the active substance and the propellant to mix together, creating the inhalation solution. For the aerosol drug in Proventil® HFA, oleic acid and ethanol compose the surfactant [13]. However, as mass of the surfactant is approximately 10% of the active substance (less than 0.01% of the total mass of the inhaler), the surfactant was considered negligible and was excluded from the model.

2.2.4. Metering Valve

The metering valve controls the dose of drug released in a single inhaler puff. It consists of the ferrule, ferrule gasket, valve stem, compression spring, tank, bottle emptier, diaphragm, and tank seal.

Stamping was used to model production of the aluminum ferrule in GaBi. The ferrule gasket was modeled as polyethylene composition manufactured by using injection molding. The valve stem, spring, tank, and bottle emptier were modeled as 316 stainless steel material. While valve stems can be manufactured using metal injection molding [17,18], this process is not built into the GaBi database, so deep drawing was used instead. The compression spring is manufactured using an auto-coiling machine, which has a similar energy consumption to steel stamping and bending, as employed in the GaBi model. The tank and bottle emptier are manufactured via press forming, which was assumed to be similar to stamping and bending, as used in the GaBi model. Nitrile rubber is used to produce the diaphragm and tank seal. In GaBi, the rubber was modeled as a blend of 50% acrylonitrile and 50% butadiene (the acrylonitrile content in rubber typically ranges from 20–50%) [19,20]. The polymerization process was condensed into a single phase and was assumed to have a similar energy consumption to the acrylonitrile-butadiene-styrene copolymer resin in GaBi [21]. The mass of the tank seal was less than 0.01 g (<0.04% of the total mass of the inhaler), and was thus assumed to be negligible and was excluded in the model.

2.2.5. Actuator

The actuator (which controls the inhaler movement) and actuator cap were modeled as polypropylene parts manufactured using plastic injection molding.

2.2.6. Canister

The canister containing the drug was modeled using aluminum deep drawing manufacturing. To prevent the albuterol sulfate and HFA-134a from reacting with the aluminum, the interior surface of the canister and valve components are coated with a thin dual-layer coating (<1 μm) consisting of a vapor-deposited inorganic layer and a fluorine layer [22]. The mass of the coating in the device is negligible, and was thus excluded from the model.

2.2.7. Use Phase

During the inhaler's use phase, the medicine canister is placed into the actuator and the device is primed by shaking before use. A single dose of the drug is administered in the form of two puffs of the inhaler. In the GaBi LCA model, the sole input for the use phase was the inhaler itself. All of the propellant associated with each puff was assumed to be released to the atmosphere (i.e., no absorption of the propellant itself in the body in this conservative model), with an associated GWP impact.

2.3. Inventory Analysis: Electric Nebulizer

An inventory of the components of the DeVilbiss Pulmo-Aide® nebulizer was produced by disassembling the device and determining the mass and major composition of each component, as listed in Table 2. The major components of the nebulizer were grouped into the active substance (as described previously), exterior shell, stator (including core, coils and cover), rotor (including squirrel cage, ball bearings, and central shaft), suction chamber, fan (including fan, fan housing, and cross brace), medicine delivery (including mouthpiece, medical tubing, and medicine chamber), and power cord.

Table 2. Components of the electric nebulizer (EN) including mass (total of 2726 g), composition, and manufacturing process used in the life cycle assessment (LCA) model.

Major Components of the EN	Mass (g)	Composition	GaBi Model Manufacturing Process
Active Substance	0.003 [2]	Albuterol Sulfate	N/A [1]
Exterior Shell	1102	Acrylonitrile Butadiene Styrene (ABS)	Plastic Injection Molding
Stator			
Core	539	Steel	Casting
Coils	135	Copper	Wire Drawing
Cover	182	Steel	Stamping and Bending
Rotor			
Squirrel Cage	288	Aluminum	Casting
Ball Bearings & Central Shaft	124	Stainless Steel	Casting
Suction Chamber	510	Aluminum	Casting
Fan			
Fan	16	Polyvinyl Chloride (PVC)	Plastic Injection Molding
Fan Housing	148	PVC	Plastic Injection Molding
Cross Brace	37	Steel	Stamping and Bending
Medicine Delivery			
Mouthpiece	19	Polypropylene	Plastic Injection Molding
Medical Tubing	41	PVC	Extrusion
Medicine Chamber	12	Polymethylmethacrylate (PMMA)	Plastic Injection Molding
Power Cord	112	70% Copper / 30% PVC	Wire Drawing/Extrusion

[1] Not applicable (N/A) as the manufacturing process was modeled as directly combining the materials to output the component using 0.11 MJ assembly energy input/device; [2] For a single dose.

Throughout the model, it was assumed that the DeVilbiss Pulmo-Aide® nebulizer was constructed out of lightweight, durable, and easily accessible materials to keep costs to a minimum. Additional assumptions for the manufacturing and assembly of each component were made to accommodate the LCA model by using the processes available in the GaBi database, as described in the following sections. An assembly energy of 0.1 MJ (0.0005 MJ/dose) was used to represent manufacturing based on other manufacturing processes built into GaBi.

2.3.1. Active Substance: Albuterol Inhalation Solution

A single dose of the albuterol sulfate inhalation solution used during device operation contains 0.003 g of albuterol sulfate, 3 g of sterile saline, and 0.000049 g of 96% sulfuric acid used to adjust the pH from 7 to 4. The saline solution was modeled using deionized water and sodium chloride. The solution production process included an input of 335 kJ thermal energy, as calculated to dissolve the sodium chloride using the specific heat of water and the required change in temperature from room temperature to boiling.

2.3.2. Exterior Shell

The outer shell of the nebulizer consists of three separate parts, all of which are composed of the same material, and was thus modeled as a single part. Acrylonitrile butadiene styrene (ABS) material was used to model the manufacture of the exterior shell via plastic injection molding.

2.3.3. Stator: Core, Coils and Cover

The motor's core was manufactured using multiple steel sheets. The manufacturing process was simplified in the GaBi model by representing the mass of the steel in the core as 80% of the combined mass of the stator's core and coils. The copper coils (remaining 20% of the combined mass) were modeled by using wire drawing manufacturing. The coils and core were coated with a laminate to improve the efficiency of the induction motor, but this coating was excluded from the model as its mass was negligible in comparison to the total mass. The cover was modeled as steel, which was bent, welded together, and press formed around the stator.

2.3.4. Rotor: Squirrel Cage and Ball Bearings & Central Drive Shaft

The rotor's squirrel cage was assumed to be aluminum rather than copper composition because it would offer a less expensive option. Rotor manufacturing was modeled by using the common die casting process [23,24]. The mass of the squirrel cage (electromagnets) was assumed to be 70% of the rotor's mass, while the other 30% consisted of the ball bearings and the central drive shaft. The central drive shaft is inserted into the rotor squirrel cage when it is hot, which allows it to shrink onto the shaft and have a firm fit. The modeling assumption was that 0.1 MJ of electricity was input into the system to manufacture the ball bearings and the central shaft.

2.3.5. Suction Chamber

The suction chamber was simplified by assuming it was constructed using die casting with only aluminum materials. The rubber seal weighed less than 0.01 g (<0.0003% of device mass), and was thus assumed to be negligible in the model.

2.3.6. Fan: Fan, Fan Housing, and Cross Brace

The fan and housing for the fan were modeled using polyvinyl chloride (PVC) granulates to manufacture the parts using plastic injection molding. The cross brace was manufactured using steel and was modeled using a stamping and bending method.

2.3.7. Medicine Delivery: Mouthpiece, Medical Tubing, and Medicine Chamber

The materials used to model the mouthpiece, medical tubing, and medicine chamber were polypropylene, PVC, and polymethylmethacrylate (PMMA), respectively. The mouthpiece and medicine chamber manufacturing were modeled using plastic injection molding, while manufacturing of the medical tubing was modeled using extrusion.

2.3.8. Power Cord

The power cord was modeled as copper wire surrounded by PVC tubing, with the relative composition of the materials consisting of 70% PVC and 30% copper. In the model, the PVC tubing was manufactured by extrusion and the copper wiring was manufactured by wire drawing. The electricity required to manufacture the power cord was assumed to be 0.1 MJ based on other manufacturing processes in GaBi.

2.3.9. Use Phase

During the use phase of the nebulizer, the device was modeled as requiring 60 W of power for 15 min.

Unlike the inhaler, which cannot be reused after the drug is spent, a single nebulizer is used numerous times over its lifespan. The mouthpiece and medicine delivery components are cleaned between each use. In this study, two different approaches to cleaning were modeled as a part of the use phase: (1) using a dishwasher; and (2) hand cleaning. The model used a 1800 W dishwasher for one hour, requiring 15 L (4 gallons) of tap water. All of the tap water inputs were modeled as sourced from surface water, which is a more conservative source as it typically requires a higher degree of treatment than groundwater. A full-capacity dishwater was assumed to use 10 g of soap. In the GaBi model, the soap was modeled as glycerin, which is one of the products of saponification (the chemical process used to produce soap). The mouthpiece was assumed to take up 1% of the dishwasher volume, and materials and energy were allocated accordingly.

When the nebulizer mouthpiece was hand washed, it was assumed that 1 g of soap was used. Additionally, 7.6 L (2 gallons) of tap water was used per minute, and 1 min was assumed for device cleaning. After hand washing, the mouthpiece and medicine chamber are sterilized in a vinegar solution composed of one part acetic acid (5% acidity vinegar) to three parts water. In the model, the vinegar solution was composed of 100 g of vinegar and 300 g of tap water.

2.4. Impact Assessment

After using the inventory analysis to develop complete GaBi models representing the cradle-to-use phases of the inhaler and nebulizer, a comparative impact assessment of GWP was performed using the material and energy flows and environmental impacts as defined in the GaBi database. In accordance with the ISO 14040 [7], normalization and weighting are optional components of impact assessment, and were therefore omitted from this analysis.

2.5. Statistics

Together with the baseline scenario (best data approximations), the best and worst case uncertainty scenarios ($\pm 100\times$ uncertain parameters) provided three data points from which statistics were computed at a confidence level of $\alpha = 0.05$. The small sample size preempted tests for normal distributions; however, ANOVA and Tukey post hoc tests, which assume normal distributions, were used to test for statistically significant differences in the devices' GWPs. All of the statistics were performed using GraphPad Prism software.

3. Results and Discussion

The total GWP of the inhaler in comparison to the nebulizer, cleaned using a dishwasher or via hand washing, is shown in Figure 1. The bars represent the baseline scenario, using best estimates and assumptions for all of the input parameters. The inhaler had significantly higher GWP than the nebulizer, and cleaning the nebulizer by hand washing was associated with greater GWP than cleaning it in the dishwasher. These differences arose from the use phase, whereas the pre-use phase, consisting of the extraction, production and manufacture, was statistically indistinguishable among the devices (and identical for the two nebulizer scenarios), $p > 0.05$.

The use phase constituted the majority of the GWP for the inhaler and hand washed nebulizer: 98% and 60%, respectively, whereas the use phase accounted for 40% of the dishwashed nebulizer's GWP. For the inhaler, the use phase consists of two puffs of the inhaler, which releases HFA-134a to the atmosphere. The results demonstrate that the inhaler's HFA-134a propellant has a substantial environmental impact, which aligned with the initial study hypothesis. The use-phase difference between the nebulizer scenarios using hand washing vs. dishwashing was due to the vinegar cleaner and greater amount of water needed for handwashing.
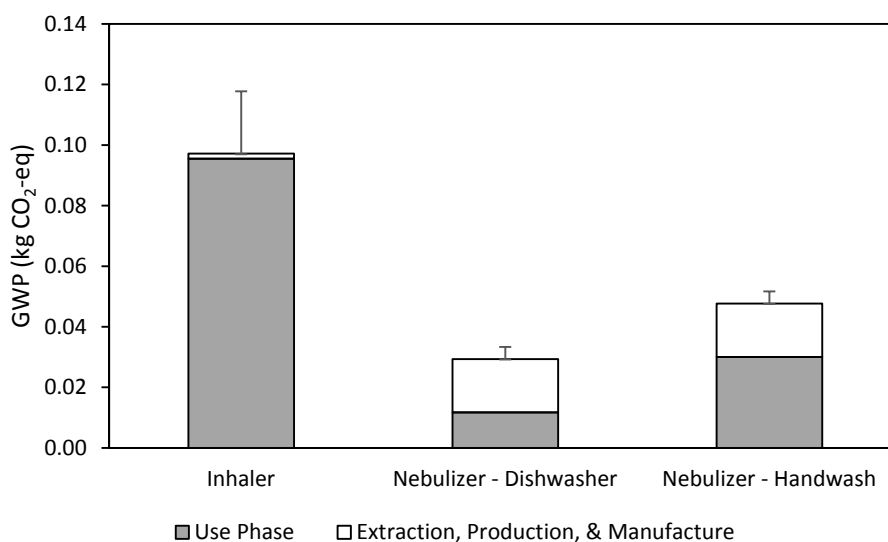
Figure 1. Total cradle-to-use phase global warming potential (GWP) of the inhaler compared to the nebulizer (cleaned using a dishwasher in comparison to hand washing). The bars illustrate the baseline assessment, while the error bars signify the uncertainty analysis using $\pm 100 \times$ inputs for the most uncertain parameters.

The amount of albuterol per nebulizer treatment is substantially higher than that for an inhaler, 3 mg versus 200 μg. Therefore, this study's findings may be limited if the GWP associated with manufacturing albuterol is higher than the conservative, high GWP HCFC-22 placeholder used in the GaBi model. Even using HCFC-22 to model albuterol, the dose of medicine represented a very small component of the overall GWP in all of the treatment scenarios. Thus, it is likely that differences in the amount of albuterol for the two different delivery devices do not impact the overall GWP of those treatments.

3.1. Uncertainty Analysis

An uncertainty analysis was used to explore the potential influences of variable inputs. The best and worst case scenarios are illustrated by the error bars in Figure 1 (worst case: increasing all uncertain parameters $100 \times$; best case: decreasing all uncertain parameters $100 \times$). The greatest uncertainty in the

analysis stemmed from assumptions made about the individual component manufacturing processes, as detailed in the following sections. The GWP of the device scenarios relative to the others did not change, even assuming very high ($\pm 100 \times$s) variation in input parameters.

3.2. Inhaler

The majority of the uncertainty in the inhaler LCA values was associated with the details concerning the manufacturing processes, including the compressed air for albuterol sulfate production, the electricity and compressed air for the ferrule, the electricity for the spring, the electricity and thermal energy for the valve stem, and the electricity for nitrile rubber components. As part of the uncertainty analysis, $\pm 100 \times$s differences in these manufacturing input values were evaluated. As shown in Figure 1, $100 \times$ increase in all uncertain values (worst case) increased the inhaler's total GWP by 21%, while $100 \times$ decrease (best case) led to 0.2% reduction in GWP.

Figure 2 illustrates the influence of uncertainty on the relative distribution of GWP by inhaler component. In the $+100 \times$s uncertainty scenario, the production of the spring (part of the metering valve) represented the major difference in the relative distribution, and in the total GWP, as its GWP alone increased by 93%. This large increase in GWP was surprising because the spring has a small mass compared to the rest of the MDI components.
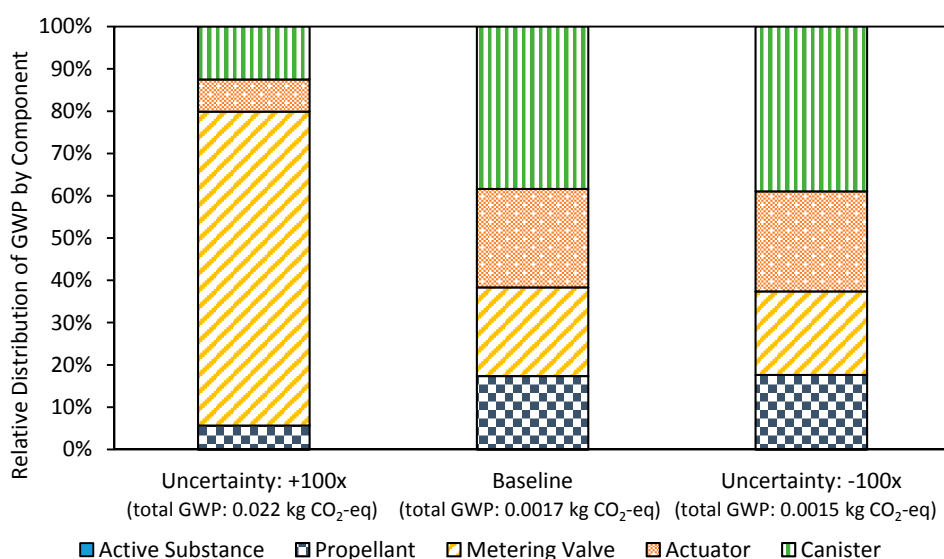

Figure 2. Relative distribution of global warming potential (GWP) associated with the major components of the metered dose inhaler. The three scenarios shown represent the baseline case using best estimates and assumptions, a worst case ($100 \times$ increase in uncertain parameter inputs), and a best case ($100 \times$ decrease in uncertain parameter inputs). Note that the GWP associated with the active substance was small compared to other components, and is not visible in the figure.

In addition to the uncertainty associated with the quantitative inputs noted above, uncertainty in the LCA model stemmed mainly from the processes used for production of albuterol and the polymerization process of nitrile rubber. Throughout the analysis, HCFC-22 was used as the placeholder for albuterol sulfate. This modeling approach clearly introduced inaccuracy into the absolute values of the LCA model outputs; however, the GWP associated with albuterol production was not appreciable in the analysis as it was quite small in comparison to other components.

The nitrile rubber manufacturing process includes six phases (polymerization, recovery, blending, coagulation, dewatering, and drying [21]), but was simplified into a single phase because the details of the inputs and outputs of each phase could not be accurately determined. Several of the manufacturing processes, such as aluminum sheet stamping and bending, stainless steel deep drawing, and auto

coiling were not available in GaBi; thus, the values for the inputs and outputs were obtained from similar processes built into the database. The aluminum sheet stamping and bending values were modeled after the steel sheet stamping and bending process. As aluminum is less dense than steel, some of these values may actually be less. The opposite may be true for the stainless steel deep drawing, where the GaBi-defined aluminum deep drawing process was used as the model for the steel process. Auto coiling is essentially a machine that bends a steel wire into a spring, so it was represented in the model as a stamping and bending process.

The materials and associated manufacturing processes for the HFA 134a propellant and the polypropylene, steel, and aluminum components were readily available in the GaBi database; thus the modeling of these components was associated with low uncertainty.

3.3. Nebulizer

The greatest uncertainty in the nebulizer data arose from the quantities of electricity needed for the manufacturing of components including the stator coils and core, parts of the rotor (ball bearings and central drive shaft), power cord, and assembly of the nebulizer. As shown in Figure 1, a 100× increase in all uncertain parameters (worst case) increased the inhaler's GWP by 8% (14% for the dishwashing scenario), while a 100× decrease (best case) led to 0.3% reduction in GWP (0.4% for the dishwashing scenario). Figure 3 illustrates that the relative distribution of GWP by nebulizer component remained relatively constant as uncertain parameters varied. This suggests that the LCA outcome may not be particularly sensitive to any given uncertain parameter.
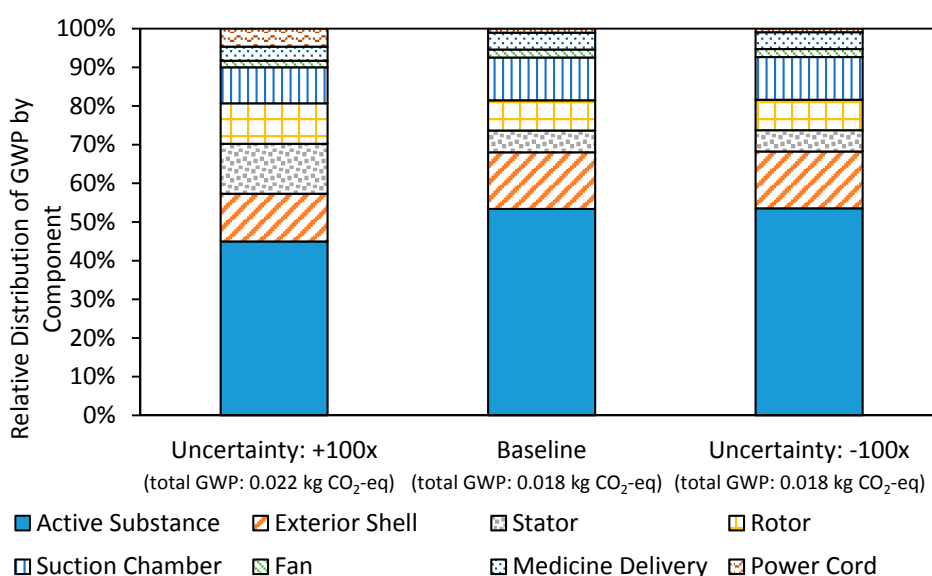

Figure 3. Relative distribution of global warming potential (GWP) associated with the major components of the electric nebulizer. The three scenarios shown represent the baseline case using best estimates and assumptions, a worst case (100× increase in uncertain parameter inputs), and a best case (100× decrease in uncertain parameter inputs).

In addition to the uncertainty associated in the quantitative inputs noted above, the bulk of the uncertainty associated with the nebulizer analysis was attributed to the manufacturing of the induction motor. Most of the motor processes were not built into the GaBi database, so it was assumed that the system inputs included the constituent material (e.g., steel or PVC) and electricity, with an output of the respective nebulizer component. This assumption was made for the stator coils, stator core, power cord, ball bearings, central drive shaft, and the assembly of the entire device.

3.4. Breakeven Analysis

A breakeven analysis was performed to determine the point of GWP equivalency between cleaning the nebulizer mouthpiece using dishwashing versus by hand washing (Figure 4). Using the baseline case (best estimates and assumptions), when the mouthpiece accounted for 10.3% of the dishwasher load, the use phase GWP for dishwashing was equivalent to the use phase GWP for hand washing. Accordingly, when cleaning the mouthpiece as part of a full dishwasher load (mouthpiece accounting for <10.3% of the load), dishwashing was more effective. However, less GWP resulted from handwashing the mouthpiece in comparison to washing it in a relatively empty dishwasher (mouthpiece accounting for >10.3% of the load). In the event that the amount of soap and water used for handwashing doubled, the breakeven point was 17.0% of the dishwasher's load allocated for the mouthpiece (i.e., the dishwasher was more effective comparatively). Alternately, 7.0% was the breakeven point for the mouthpiece's allocation of the dishwasher load when hand washing inputs of soap and water were both halved.
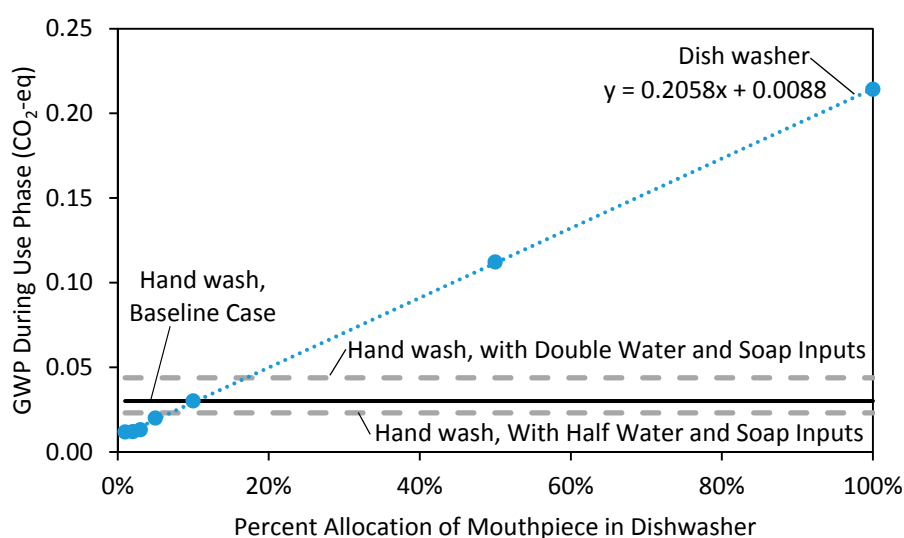
Figure 4. Breakeven analysis showing the global warming potential (GWP) of the nebulizer cleaned in the dishwasher as a function of proportion of dishwasher space allocated for the mouthpiece. The horizontal lines represent three hand washed mouthpiece scenarios: baseline case using best estimates and assumptions, double water and soap inputs, and half water and soap inputs.

4. Conclusions

Medical device manufacturers can benefit from using life cycle assessment (LCA) to optimize processes and develop more eco-friendly alternatives. LCAs may also be of use to healthcare providers choosing between equivalent treatment options by helping them to consider the environmental impact of public health practices. This comparative LCA demonstrated that the Proventil® HFA inhaler accounts for significantly greater cradle to use global warming potential (GWP) than the DeVilbiss Pulmo-Aide® electric nebulizer. The inhaler's GWP, 0.0972 kg CO_2-eq, was greater than the nebulizer's even when uncertain parameters were varied ±100×. This finding is based on the conservative estimate of equivalency between two inhaler puffs and a single nebulizer treatment, whereas disproportionately more puffs are often needed in treatments of more severe asthma exacerbations. The total GWP for the electric nebulizer was 0.0294 kg CO_2-eq, assuming that the mouthpiece was cleaned in a dishwasher, while it was 0.0477 kg CO_2-eq when the nebulizer mouthpiece was hand washed between uses. No statistical difference was observed in the devices' pre-use (extraction, production, and manufacturing) phase. The use phase of the inhaler accounted for 96% of the GWP, stemming from the release of the HFA 134a propellant used to deliver the drug. When uncertain parameters were

adjusted $\pm 100\times$, the trend in GWP among the scenarios modeled, inhaler > hand washed nebulizer > dishwashed nebulizer remained consistent. When the mouthpiece of the nebulizer accounted for 10% of a dishwasher load, it broke even with the GWP of the hand washed scenario (7–17% of the dishwasher load using scenarios with double and half use of soap and water during handwashing, respectively).

References

1. World Health Organization. WHO Calls for Urgent Action to Protect Health from Climate Change. 2016. Available online: http://www.who.int/globalchange/global-campaign/cop21/en/ (accessed on 9 June 2017).
2. Chung, J.W.; Meltzer, D.O. Estimate of the carbon footprint of the US health care sector. *J. Am. Med. Assoc.* **2009**, *302*, 1970–1972. [CrossRef] [PubMed]
3. Sherman, J.; Le, C.; Eckelman, M. Life cycle greenhouse gas emissions of anesthetic drugs. *Anesth. Analg.* **2012**, *114*, 1086–1090. [CrossRef] [PubMed]
4. Hertwich, E.G.; Peters, G.P. Carbon footprint of nations: A global, trade-linked analysis. *Environ. Sci. Technol.* **2009**, *43*, 6414–6420. [CrossRef] [PubMed]
5. Thiel, C.L.; Eckelman, M.; Guido, R.; Huddleston, M.; Landis, A.E.; Sherman, J.; Shrake, S.O.; Copley-woods, N.; Bilec, M.M. Environmental impacts of surgical procedures: Life cycle assessment of hysterectomy in the United States. *Environ. Sci. Technol.* **2015**, *49*, 1779–1786. [CrossRef] [PubMed]
6. Eckelman, M.; Mosher, M.; Sherman, J. Comparative life cycle assessment of disposable and reusable laryngeal mask airways. *Anesth. Analg.* **2012**, *114*, 1067–1072. [CrossRef] [PubMed]
7. ISO. *Environmental Mangement—Life Cycle Assessment—Principles and Framework*, 2nd ed.; International Organization for Standardization: Genève, The Switzerland, 2006.
8. Aït-Khaled, N.; Enarson, D.; Bousquet, J. Chronic respiratory diseases in developing countries: The burden and strategies for prevention and management. *Bull. World Health Organ.* **2001**, *79*, 971–979. [CrossRef] [PubMed]
9. Lozano, R.; Naghavi, M.; Foreman, K.; Lim, S.; Shibuya, K.; Aboyans, V.; Abraham, J.; Adair, T.; Aggarwal, R.; Ahn, S.Y.; et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: A systematic analysis for the Global Burden of Disease Study 2010. *Lancet* **2012**, *380*, 2095–2128. [CrossRef]
10. Burney, P.; Jarvis, D.; Perez-Padilla, R. The global burden of chronic respiratory disease in adults. *Int. J. Tuberc. Lung Dis.* **2015**, *19*, 10–20. [CrossRef] [PubMed]
11. Patel, J.G.; Nagar, S.P.; Dalal, A.A. Indirect costs in chronic obstructive pulmonary disease: A review of the economic burden on employers and individuals in the United States. *Int. J. Chron. Obstr. Pulm. Dis.* **2014**, *9*, 289–300. [CrossRef] [PubMed]
12. DeVilbiss Healthcare. Pulmo-Aide(R) Compressor Nebulizer System. Available online: https://www.bpimedicalsupply.com/mm5/pdf/devilbiss-pulmoaide-compressor.pdf (accessed on 5 December 2016).
13. Purewal, T.S.; Grant, D.J.W. *Metered Dose Inhaler Technology*, 1st ed.; Interpharm/CRC: Boca Raton, FL, USA, 1998.
14. Corr, S.; Noakes, T.J. Composition Comprising Salbutamol Sulphate. Patent WO2,013,054,135, 18 April 2013.

15. Mok, Y.S.; Lee, S.; Chang, M.S. Destruction of chlorodifluoromethane (CHF2Cl) by using dielectric barrier discharge plasma. *IEEE Trans. Plasma Sci.* **2009**, *37*, 449–455.

16. Barker, P.; Cary, R.; Dobson, S. *Concise International Chemical Assessment Document 11: 1,1,1,2-Tetrafluoroethane*; World Health Organization: Geneva, Switzerland, 1998.

17. Sivigny, M.B.; Hodson, P.D. Manufacture of Metered Dose Valve Components 2010. U.S. Patent US20100300437 A1, 2 December 2010.

18. Low, D.; Li, L.; Bradley, L. Manufacture of Valve Stems 2005. U.S. Patent US20050248060 A1, 10 November 2005.

19. Morrow, N.L. The industrial production and use of 1,3-butadiene. *Environ. Health Perspect.* **1990**, *86*, 7–8. [CrossRef] [PubMed]

20. EPA. *Locating and Estimating Air Emissions from Sources of Acrylonitrile*; U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards: Washington, DC, USA, 1984.

21. Grimm, D.C. Method for the Production of Nitrile Rubber 1998. U.S. Patent US5708132 A, 13 January 1998.

22. Stein, S.W.; Sheth, P.; Hodson, P.D.; Myrdal, P.B. Advances in metered dose inhaler technology: Hardware development. *AAPS PharmSciTech* **2014**, *15*, 326–338. [CrossRef] [PubMed]

23. Finley, W.R.; Hodowanec, M.M. Selection of copper versus aluminum rotors for induction motors. *IEEE Trans. Ind. Appl.* **2001**, *37*, 1563–1573. [CrossRef]

24. Mechler, G.C. *Manufacturing and Cost Analysis for Aluminum and Copper die Cast Induction Motors for GM's Powertrain and R&D Divisions*; Massachusetts Institute of Technology: Cambridge, MA, USA, 2010.