Medication Nebulizer Performance*

Effects Of Diluent Volume, Nebulizer Flow, and Nebulizer Brand

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Background: Medication nebulizers are commonly used to deliver aerosolized medications to patients with respiratory disease. We evaluated output and respirable aerosol available to the patient (inhaled mass) for 17 medication nebulizers using a spontaneous breathing lung model.

Methods: Three nebulizer fill volumes (3, 4, and 5 mL containing 2.5 mg of albuterol) and 3 oxygen flows (6, 8, and 10 L/min) were evaluated using the 17 nebulizers. A cotton plug at the nebulizer mouthpiece was used to trap aerosol during simulated spontaneous breathing. Following each trial, the amount of albuterol remaining in the nebulizer and the amount deposited in the cotton plug were determined spectrophotometrically. Aerosol particle size was determined using a 11-stage cascade impactor.

Results: Increasing fill volume decreased the amount of albuterol trapped in the dead volume (p<0.001) and increased the amount delivered to the patient (p<0.001). Increasing flow increased the mass output of particles in the respirable range of 1 to 5 μm (p=0.004), but the respirable mass delivered to the patient was affected to a greater extent by nebulizer brand (p<0.001) than flow. Although 2.5 mg of albuterol was placed into the nebulizers, less than 0.5 mg in the respirable range of 1 to 5 μm was delivered to the mouthpiece.

Conclusions: The performance of medication nebulizers is affected by fill volume, flow, and nebulizer brand. When they are used for research applications, the nebulizer characteristics must be evaluated and reported for the conditions used in the investigation. (CHEST 1996; 110:498-505)

Key words: aerosol therapy; inhaled bronchodilator administration; nebulizers

Abbreviations: GSD=geometric standard deviation; MMAD=mass median aerodynamic diameter

Despite the common use of metered-dose inhalers and the availability of dry powder inhalers, aerosolized medications are still frequently administered by nebulizer. Nebulizers are commonly used for inhaled bronchodilator administration to patients with reactive airways, including the perioperative and postoperative treatment of these patients. Advantages of nebulizers include the ability to use them with patients who cannot coordinate the use of a metered-dose inhaler1 and the ability to conveniently administer a large (or continuous) dose into the lungs.2 Important characteristics of nebulizer performance include the drug output, the aerosol particle size generated, the nebulization time, and the amount of drug delivered to the patient. Factors that have been shown to affect nebulizer performance include device construction (ie, manufacturer), fill volume, flow, temperature, and humidity of the driving gas.1

A common feature of nebulizers is dead volume, which is the volume of solution that remains in the nebulizer cup after aerosol production ends. Previous studies have typically evaluated dead volume by serial weighing.3-5 This method does not adequately characterize drug output and amount of drug in the dead volume due to reconstitution in the nebulizer cup.6-7 Reconstitution occurs because of evaporation owning to the low relative humidity of the gas powering the nebulizer. Nebulizer output should be determined more appropriately by measuring the amount of medication that remains after aerosol production is complete.

Particle size is an important characteristic of nebulizer performance. Particles too large do not reach the
lower respiratory tract, whereas particles too small are exhaled. It has been shown that smaller particles are produced at higher nebulizer flows. Methods that determine particle sizes from nebulizers should classify them according to aerodynamic diameter and not physical diameter. A cascade impactor, unlike the optical laser particle counter, allows quantification of drug delivery in terms of aerodynamic size characteristics of the aerosol. Aerodynamic diameter accounts for the density and irregular shape of drug particles and more accurately predicts the behavior of the aerosol as it is delivered to the patient.

Loffert et al. introduced the concept of respirable rate, which combines the effects of nebulizer output, nebulization time, and percent of particles in the respirable range. However, they determined nebulizer output by serial weighing rather than measurement of the amount of nebulized medication. A more useful index of nebulizer function might be respirable mass—the amount of aerosolized drug in the respirable range. In this study, we extended the concept of Loffert et al. by quantifying not only the respirable aerosol mass from the nebulizer, but also the respiratory aerosol mass made available to the patient at a specific ventilatory pattern.

It has been suggested that nebulizers be characterized by the amount of medication that is delivered to the patient. Smaldone introduced the term inhaled mass, which he defined as that mass of drug actually delivered by a given nebulizer for a defined breathing pattern and period of time. Inhaled mass is affected not only by the performance of the nebulizer, but also by the breathing pattern chosen. For a given breathing pattern, inhaled mass should allow comparison of the quantity of drug delivered by different nebulizer systems and adjustment of the drug dose accordingly. To our knowledge, evaluation of inhaled mass has not been reported for nebulizers designed primarily for delivery of bronchodilators.

We conducted this study to evaluate medication nebulizer performance addressing those issues described above. Dead volume, the amount of drug remaining in the dead volume, nebulization time, and aerosol available to the patient (inhaled mass) were evaluated for 17 nebulizers, 3 fill volumes, and 3 flows. We also evaluated particle size for 3 flows with the 17 nebulizers at a single fill volume.

**Table 1—Nebulizer Brands Evaluated**

<table>
<thead>
<tr>
<th>Nebulizer Brand; Manufacturer; Location</th>
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<tbody>
<tr>
<td>A. Whisper Jet Nebulizer System; Marquest Medical Products Inc; Englewood, Colo</td>
</tr>
<tr>
<td>B. Ava-Neb Nebulizer; Hudson Respiratory Care Inc; Temecula, Calif</td>
</tr>
<tr>
<td>C. Raindrop Medication Nebulizer; Puritan-Bennett; Lena, Kan</td>
</tr>
<tr>
<td>D. Via One Nebulizer; Westmed Inc; Tucson, Ariz</td>
</tr>
<tr>
<td>E. Sidestream Disposables; Inspired Medical Products; Pagham, West Sussex, UK</td>
</tr>
<tr>
<td>F. T-UpDraft II Neb-U-Mist Nebulizer; Hudson Respiratory Care Inc; Temecula, Calif</td>
</tr>
<tr>
<td>G. Fan Jet Nebulizer; Westmed Inc; Tucson, Ariz</td>
</tr>
<tr>
<td>H. One-No 8900 TG; Salter Labs; Arvin, Calif</td>
</tr>
<tr>
<td>I. Airlife Misty Neb; Baxter Healthcare Corp; Valencia, Calif</td>
</tr>
<tr>
<td>J. Hospital; Lindenhurst, NY</td>
</tr>
<tr>
<td>K. T-UpDraft; Hudson Respiratory Care Inc; Temecula, Calif</td>
</tr>
<tr>
<td>L. Sidestream Disposable; Inspired Medical Products; Pagham, West Sussex, UK</td>
</tr>
<tr>
<td>M. Intertech Inspiron; Intertech Resources Inc; Lincolnshire, Ill</td>
</tr>
<tr>
<td>N. Betamist Nebulizer; Professional Medical Products Inc; Greenwood, SC</td>
</tr>
<tr>
<td>O. Micro-Mist; Hudson Respiratory Care Inc; Temecula, Calif</td>
</tr>
<tr>
<td>P. Ventstream; Inspired Medical Products; Pagham, West Sussex, UK</td>
</tr>
<tr>
<td>Q. B &amp; F Medical Products Inc; Toledo, Ohio</td>
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**Materials and Methods**

**Nebulizers Evaluated**

We evaluated 17 commercially available nebulizers (Table 1). Nebulizers were provided by their manufacturers. All units were from the same lot number and the same packaging case. The nebulizers were provided by the manufacturer from their saleable stock; none were prototypes or otherwise prepared specifically for this study, and all were used as supplied from the manufacturer.
Evaluation of Dead Volume and Aerosol Available to the Patient

The experimental system is shown in Figure 1. The nebulizer was placed in a clamp and attached to a ring stand in the vertical position. A double-sided test lung (Michigan Instruments; Grand Rapids, Mich) was used to simulate spontaneous breathing. One side of the test lung was attached to a ventilator (Puritan-Bennett 7200 ventilator; Puritan-Bennett; Carlsbad, Calif) and that side of the test lung lifted the contralateral side to simulate spontaneous breathing. The lung model was set to simulate breathing at 12 breaths/min, tidal volume approximately 0.45 to 0.5 L, inspiratory flow approximately 0.3 to 0.4 L/s with a sine wave pattern, and tidal volume approximately 0.45 to 0.5 L. A pilot evaluation showed that this closely simulated the breathing pattern of a normal volunteer breathing through a mouthpiece without nose clips (imitating mouthpiece breathing with a nebulizer).

The mouthpiece of the nebulizer was replaced with a step-down adapter and a cotton plug was placed into the adapter to trap aerosol. Pilot testing using several cotton plugs showed that a single plug was 100% effective as a filter of aerosol from the nebulizer. The test chamber of the lung model (simulating a spontaneously breathing patient) was attached to the adapter containing the cotton plug. Saline solution diluent volumes of 2.5, 3.5, and 4.5 mL, and 2.5 mg (0.5 mL of 0.5% of albuterol [Proventil; Schering; Kenilworth, NJ] were placed into the nebulizer cup to produce fill volumes of 3, 4, and 5 mL. Saline solution and albuterol were precisely measured using calibrated syringes. Oxygen flows of 6, 8, and 10 L/min were used from a calibrated flowmeter (Timeter; Lancaster, Pa) connected to the hospital bulk oxygen supply. Three new nebulizers of each type were evaluated at each combination of diluent volume and oxygen flow. All evaluations were conducted at ambient room temperature (approximately 22°C) and humidity (approximately 40 to 50% relative humidity).

The nebulizer was tapped periodically during each trial. Nebulization time was determined by a stopwatch and was considered complete when there was no visible or audible evidence of nebulization for a period of 30 s. The nebulizer was weighted empty (Ohaus 311 Cent-O-Gram Balance; Carolina Biological; Burlington, NC), after it was filled with medication and diluent, and at the end of the trial. The percentage of solution that was nebulized was calculated from these mass values.

At the end of each trial, the amount of drug remaining in the nebulizer cup was determined by washing the inside of the nebulizer cup with 10 mL of saline solution and spectrophotometrically determining the amount of albuterol remaining in the nebulizer cup. The drug present in the cotton plug was extracted using 20 mL of saline solution and gentle agitation by vortex. The resulting solution was centrifuged at 5000 g for 10 min to remove all cotton fibers from the solution and the amount of albuterol was then determined spectrophotometrically. As with other studies using methods similar to ours, we assumed that all albuterol was extracted from the cotton.

Particle Size Determination

The experimental setup used to determine particle size is shown in Figure 1. During evaluation, the nebulizer was placed in a clamp and attached to a ring stand in the vertical position. Albuterol (0.5 mL of 0.5%) was placed into the nebulizer cup and diluted with 2.5 mL of saline solution. Particle sizes were determined at oxygen flows of 6, 8, and 10 L/min. Three new nebulizers of each type were evaluated at each oxygen flow.

Aerosol particle size produced by the nebulizer was determined using an 11-stage cascade impactor (Intox; Albuquerque, NM) with cutoff stages of 12, 9.52, 7.56, 6, 5, 4, 3, 1.8, 1, 0.4, and 0.25 μm. Aerosol was sampled 15 cm from the outlet of the nebulizer at a flow of 2 L/min to the impactor for 2 min. The albuterol deposited on each stage of the impactor was collected on plates, washed with saline solution, and the amount of albuterol was determined spectrophotometrically. The cascade impactor was calibrated by the manufacturer and used per manufacturer's specifications. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were determined from the calibration curves provided by the manufacturer. Cumulative deposition data were plotted against stage cutoff diameter, and fitted with a logarithmic regression curve to determine the particle size at 50% of the accumulated deposition (MMAD). This relationship was unimodal for all nebulizers and R² for this relationship is typically greater than 0.9 in our laboratory. GSD was calculated as the MMAD divided by the particle size at 16% deposition. In addition to MMAD and GSD, the percentage of particles in the respirable range of 1 to 5 μm was determined. Although both larger and smaller particles may have clinical benefit, we defined respirable particles as 1 to 5 μm for purposes of describing nebulizer performance in the laboratory. The same particle size range (1 to 5 μm) has been used by others to describe nebulizer performance.

Respirable Mass

We also calculated respirable mass to combine the effects of drug output and the percentage of particles in the respirable range. Drug output was calculated by subtracting the amount of medication in the dead volume from the amount of medication placed into the nebulizer at the beginning of the trial (2.5 mg). Respirable mass output of the nebulizer was then calculated by multiplying the drug output times the percentage of particles in the respirable range of 1 to 5 μm. Respirable mass available to the patient was calculated by multiplying the inhaled mass times the percentage of particles in the respirable range. Thus, respirable mass output of the nebulizer was determined...
The amount of drug in the dead volume measured by serial weighing (gravimetric method) was significantly less than that determined by measuring the amount of drug remaining in the dead volume (spectrophotometric method) (0.81±0.01 mg vs 1.14±0.01 mg; p<0.001). The effects of flow, diluent volume, and nebulizer brand on dead volume are shown in Figure 2. There was a small but significant (p=0.02) decrease in dead volume amount with an increase in flow from 6 to 10 L/min. There was no significant difference (p>0.05) between 8 and 10 L/min and 6 and 8 L/min. With an increase in diluent volume, there was a significant decrease in dead volume amount (p<0.001); this effect was significant among all levels of diluent volume. There were also significant differences in dead volume among nebulizer brands (p<0.001).

Aerosol Mass Available to the Patient (Inhaled Mass)

The effects of flow, fill volume, and nebulizer brand on the amount of aerosol available at the mouthpiece are shown in Figure 3. There was a small but significant (p=0.02) decrease in the amount of drug delivered to the mouthpiece (and thus available to the patient) with an increase in flow from 6 to 10 L/min. There was no significant difference (p>0.05) between 8 and 10 L/min and 6 and 8 L/min. There was a significantly greater amount of drug delivered to the mouthpiece with an increase in fill volume (p<0.001) from 3 to 4
mL and from 3 to 5 mL. However, there were significant differences in albuterol delivered to the mouthpiece between 4 and 5 mL. There were also significant differences among nebulizer brands in the amount of drug delivered to the mouthpiece (p<0.001).

Nebulization Time

The effects of flow, fill volume, and nebulizer brand on nebulization time are shown in Figure 4. There was a significant increase in nebulization time with an increase in volume or a decrease in nebulizer flow (p<0.001 in each case). These differences were significant between all levels of volume and nebulizer flow (p<0.05 by Scheffé analysis). There were also significant differences in nebulization time among nebulizer brands (p<0.001).

Particle Size

The effects of flow and nebulizer brand on particle size are shown in Figure 5. There was a significant decrease in MMAD with an increase in nebulizer flow (p<0.001). There were also significant differences in MMAD among nebulizer brands (p<0.001). As shown in Figure 6, there was a small, but significant (p=0.004) increase in the mass of particles in the respirable range with an increase in nebulizer flow. There were significant differences among nebulizer brands in the mass of particles in the respirable range (p<0.001). By Scheffé post hoc analysis, there was a significant difference in both MMAD and particles in the respirable range between flows of 6 and 8 L/min and between 6 and 10 L/min, but no difference between 8 and 10 L/min.

Respirable Mass

Respirable mass output of the nebulizers and respirable mass available to the patient is shown in Figure 7. With an increase in flow, there was a small but insignificant increase in respirable mass output (p=0.07) and respirable mass available to the patient (p=0.43). For nebulizer brands, there were significant differences in respirable mass output and respirable mass available to the patient (p<0.001 in each case). There was significantly more respirable aerosol mass output from each nebulizer than was available to the patient (p<0.001).

Discussion

In this study, we have demonstrated that medication nebulizer function is affected by diluent volume, flow, and nebulizer brand. Increasing diluent volume decreased the amount of albuterol trapped in the dead volume and increased the amount delivered to the patient. Increasing diluent volume also increased
nebulization time, the effect of which was offset by increased flow. Compared with the effect of diluent volume, flow had a lesser effect on nebulizer performance. Increasing flow increased the mass of particles in the respirable range of 1 to 5 μm; the respirable mass delivered to the patient was affected to a greater extent by nebulizer brand than flow. The effect of nebulizer brand was relatively greater than the effect of diluent volume or flow, with large differences among devices of different manufacturers.

A large fraction of the medication placed into the nebulizer cup remains trapped within the device and in not made available to the patient. Previous studies have evaluated this dead volume by serial weighing. However, such gravimetric methods do not account for the effect of reconcentration within the nebulizer. We found that the amount of albuterol trapped in the nebulizer is nearly 50% greater than that estimated by gravimetric methods. These results agree with those of O’Callaghan et al., who also found an overestimation of nebulizer output by 50% when serial weighing was used rather than direct measurement of nebulizer output. This can be explained by the fact that many of the particles produced within the nebulizer are baffled and return to the nebulizer cup. During this process, evaporation occurs so that particles which return to the nebulizer solution increase the concentration in the dead volume. This effect is accentuated when a cold dry gas is used to power the nebulizer, as was the case in this study.

Increasing the diluent volume increased the nebulizer output. Malone et al. used high-performance liquid chromatography to measure the amount of albuterol remaining in the nebulizer cup with 3 fill volumes (1.5, 2.5, and 3.5 mL). Similar to our findings, they found that the amount of albuterol trapped in the dead volume increased with smaller fill volumes. It is difficult to make direct comparisons between our results and those of Malone et al. They used a compressor (relative humidity approximately 50% and flow approximately 6 L/min) rather than dry oxygen to power the nebulizer; they used different fill volumes, and they used a nebulizer different than any of those in our study (DeVilbiss 646). However, they report nebulizer outputs at 2.5 mL and 3.5 mL fill volumes that are similar to what we found with fill volumes of 3 mL and 4 mL, respectively. Malone et al. also evaluated the concentration of albuterol in the nebulizer over the nebulization time and found nearly a 100% increase for smaller diluent volumes, but a smaller increase in concentration occurred for the larger diluent volume.

Studies that used gravimetric methods to evaluate nebulizer performance have also reported increased nebulizer output with increasing fill volume, as well as an increased nebulizer output with increased flow. In contrast to these findings, we found that flow had a relatively small effect on albuterol output from the nebulizer. Using three jet nebulizer brands and sodium fluoride as a tracer, Dennis et al. reported that nebulizer output was relatively unaffected by flow unless very high flows were used. Increased gravimetric output with little change in drug output as flow is increased suggests that evaporation and reconcentration are greater for higher flows.

Although flow had little effect on nebulizer output, it did affect nebulization time and particle size. A higher flow resulted in a shorter nebulization time, which could be used clinically to offset the effect of a larger diluent volume on nebulization time. Increasing the flow decreased the size of the particles generated and increased the proportion of particles in the respirable range of 1 to 5 μm. The effect of flow on particle size was greater between 6 and 8 L/min than between 8 and 10 L/min.

It is interesting to note that an increased flow did not increase the amount of drug available to the patient. When the effects of flow on both particle size and amount delivered to the patient are considered (ie,
respirable mass), there was little effect of changing flow. Increasing flow increases the number of particles in the respirable range but also increases the amount of waste during the expiratory phase so that respirable mass remains relatively constant. This is supported by previous studies. Although Clay et al20 reported a decrease in aerosol particle size when nebulizers were powered with a higher flow, others showed no difference in bronchodilator response when higher nebulizer flows were used.19,20 The lack of change in clinical response with changes in flow is likely due to our findings that respirable mass available to the patient is unchanged with changes in flow. It would thus appear that flow primarily affects nebulization time and thus higher flows are favored for convenience rather than improved drug delivery. These results also indicate that the amount of aerosol available to the patient should not be affected by use of low-flow devices like compressors that are commonly used in the home.

Differences in performance among nebulizers were greater than the differences observed for changes in diluent volume or flow. The respirable mass delivered by some nebulizers was twice that of others. From our results, it is apparent that some nebulizers have been engineered for a performance that is superior to others. The reasons for this are not readily apparent by inspection of the devices and likely relates to a number of factors, the identification of which was beyond the scope of this study. Our in vitro data are consistent with the in vivo data of Johnson et al.21 They compared deposition and physiologic response to albuterol in patients with stable asthma using a nebulizer that produced small particles (MMAD, 3.3 μm) and a nebulizer that produced large particles (MMAD, 7.7 μm). Deposition and physiologic response (ie, FEV1) were greater with the nebulizer that produced smaller particles. Presumably, the respirable mass was greater with the nebulizer that produced smaller particles.

Nebulizers can be powered only during the inspiratory phase to minimize drug waste.22,23 A system has also been described that uses a collection bag to trap aerosol particles during exhalation and delivers them to the patient on the next inspiration.24 These systems are not in common use with spontaneously breathing patients owing to their additional cost and increased complexity. Another approach to decrease waste is to boost the nebulizer output during inspiration, thus decreasing the relative amount of drug lost during the expiratory phase, and Newnham and Lipworth25 found that a nebulizer using this feature produced a twofold increase in the delivery of salbutamol to the lungs as compared with a conventional nebulizer.

Although a standard dose of 2.5 mg was placed into the nebulizer in this study, less than 0.5 mg of respirable mass was delivered to the patient. A number of the nebulizers that we evaluated delivered only a respirable mass of approximately 0.2 mg. It is of interest to note that this is similar to the standard albuterol dose delivered by metered-dose inhaler (90 mg per actuation; 2 actuations = 0.18 mg). This may explain why a number of studies have shown that clinical response using a nebulizer or metered-dose inhaler are virtually equivalent.1 When the metered-dose inhaler is used, patient performance is a major determinant of aerosol delivery. With nebulizer use, performance of the nebulizer is a major determinant of aerosol delivery.

Alvine et al26 found considerable variability in nebulizer function, not only among nebulizer brands, but also among nebulizers within specific brands. This is not particularly surprising, because nebulizers are produced in bulk and are typically short-term single-patient use devices. Our data do not allow confirmation of the results of Alvine et al,26 because we did not test enough nebulizers within each brand to address this question. Unlike Alvine et al,26 we did not find any devices that failed to function. The SEs for our data were relatively small, suggesting that variability was relatively small. An issue that requires further consideration is the function of nebulizers after repeated use, as commonly occurs in clinical practice.

As originally proposed by Smaldone,11 we believe that nebulizer function should be evaluated in a setting that parallels clinical use. The important issue is the amount of aerosol in the respirable range that is available to the patient for a defined breathing pattern. The respirable mass available to the patient cannot be predicted from the nebulizer output, and nebulizers should not be characterized on the basis of mass output alone. As shown in Figure 7, there is a poor relationship between respirable mass output of the nebulizer and respirable mass available to the patient at the ventilatory pattern we used. Respirable mass output was high and respirable mass available to the patient was relatively low for some nebulizers (eg, nebulizers E and L), whereas other nebulizers had a lower mass output but a higher mass available to the patient (eg, nebulizers D and F). Thus, characteristics in the construction of the nebulizer that affect mass output may be different from characteristics that affect respirable mass available to the patient. We evaluated only a single ventilatory pattern that we believe characterizes that of subjects spontaneously breathing through the mouth without nose clips. Further work is needed to evaluate the effect of different breathing patterns on nebulizer performance. We also believe that it is important to evaluate nebulizers using a drug solution that is similar to that used in clinical practice. For convenience, many studies in the past have used saline solution, water, or tracer materials to evaluate nebulizer performance. As demonstrated in several recent
reports, nebulizer performance is affected by the solution used.\textsuperscript{27,28} For these reasons, our results should not be extrapolated to drug solutions other than albuterol.

Ours was a laboratory study that measured aerosol delivery to the mouthpiece of the nebulizer. Actual lung deposition depends on other factors not evaluated in the study and may not correlate with the amount of aerosol delivered to the mouth for all clinical circumstances. It is also important to recognize that cascade impactor data may not reflect the actual particle size in the cascade impactor measurement, which we did not evaluate in this study.

Our results have important clinical and research implications. The most important determinant of aerosol delivery during nebulizer therapy is the specific nebulizer brand used. When nebulizers are used for research applications, the nebulizer characteristics must be evaluated and reported for the conditions used in the investigation. Changing nebulizer flow in the range of 6 to 10 L/min does not appear to affect respirable mass available to the patient, and thus a higher flow should be used to decrease treatment time. A higher diluent volume increases respirable mass and supports the use of a nebulizer fill volume of 5 mL.

Nebulizers are often considered equivalent and their performance is not considered in a rigorous manner. For metered-dose inhalers, the drug is approved with the delivery device. With nebulizers, however, the approval process for the delivery device is separate from the approval process for the drug. Further, the approval process for nebulizers does not require demonstration of a physiologic response. As we have demonstrated, the dose delivered can vary greatly among devices. Nebulizers should be considered dosing devices and not simply devices that convert a solution to an aerosol.

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REFERENCES