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CSP Deposition to the Alveolar Region of the Lung: Implications of Cigarette Design

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Ventilated cigarettes were designed to reduce the levels of smoke under machine testing conditions; however, smokers alter their smoking pattern to compensate for the reduction in yields. A relative shift in incidence of lung cancer from the more central lung airways to the alveolar region has also been associated with ventilated cigarette use. Validated mathematical models indicate that particle deposition patterns in the lung depend on particle size and inhalation behavior, including inhalation volume, flow rate, and breath-hold time. This article finds that most mathematical models underpredict total cigarette smoke particulate (CSP) deposition in the lung, likely because they do not account for coagulation, hygroscopicity, and cloud dynamics, which may increase the effective particle diameter of CSP reaching the lung tissue. The models that include these processes indicate that puff volume would be unlikely to affect particle deposition in the lung, but puff time, inhalation depth, breath-hold time, and exhalation time may affect total deposition. Most compensation appears to occur through a combination of increased puff volume and puff flow, with possible increases in inhalation depth and breath-hold time. The complex interaction between the extent of cigarette ventilation, which can affect puffing/inhalation behavior, CSP concentration, and CSP size with CSP dose to the alveolar versus more central lung airways is described. Deposition efficiency in the alveoli could plausibly be increased through compensation, but it is still unclear whether compensation could sufficiently alter patterns of CSP deposition in the lung to elicit a shift in lung cancer sites.

KEY WORDS: Cigarette design; cigarette ventilation; compensation; CSP; lung deposition

1. INTRODUCTION

Cigarette smoke is a complex mixture of chemicals composed of solid and liquid particles suspended in a gaseous phase.[1] (The common term "tar" refers to what remains of the particulate phase once water and nicotine have been removed[2]) Upon inhalation, the entrained particles can deposit at various locations in the lung, where the component chemicals may act in tumor initiation or promotion.

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Ventilated cigarette filters were designed to reduce the concentration of cigarette smoke under standard machine testing.[3] However, evidence indicates that smokers using ventilated cigarettes adjust their smoking patterns to compensate for the lower yields.[3–6] The standard machine testing protocol adopted by the Federal Trade Commission (FTC) for cigarettes does not account for the increased intensity in smoking behavior associated with compensation, such that the FTC yields for ventilated cigarettes underestimate the amount of smoke delivered under realistic smoking conditions.[7] Recent data also suggest that filter ventilation is associated with a relative increase in incidence of adenocarcinomas, which are typically located in the alveolar region of the lung,

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compared to squamous cell carcinoma, more often located in the tracheobronchial region.[8] Mathematical models and experimental evidence confirm that breathing patterns are a determinant of particle deposition patterns within the lung. However, it is currently unknown whether the compensatory shifts in smoking behavior could plausibly alter deposition patterns for cigarette smoke particles (CSP) sufficiently to cause the observed shift in cancer types.

2. METHODS

Models for predicting particle deposition in the lung, pertinent features of CSP, and characteristics of compensatory smoking are reviewed to determine whether cigarette ventilation could affect CSP deposition patterns in the lung.

The International Commission for Radiological Protection's (ICRP) human respiratory tract model[9] is used to model patterns of particle deposition under several scenarios related to compensatory smoking. The semiempirical ICRP model provides equations to calculate particle deposition to five lung compartments (two extrathoracic compartments, bronchial, bronchiolar, and alveolar) of the lung given information about particle size, density and shape factor, anatomical and physiological measures, and breathing parameters. The ICRP's "Recommended Algebraic Model for Regional Lung Deposition" (Chapter 5) for the fraction of intake inhaled and exhaled through the mouth was used to characterize the differences in alveolar deposition that might be expected under various breathing patterns.[1] The equations were solved for a series of particle sizes and the results plotted using Microsoft Excel. Reference values provided by the ICRP for an adult male were used, and particles were characterized as having a density of 1 g/m^3 and a shape factor of 1 (unitless).

Tracheobronchial, alveolar, and total lung deposition were first modeled using a tidal volume of 1,000 mL and an inspiration speed of 250 mL/sec to show that the modeling could replicate previous modeling efforts and to describe broad patterns of airways versus alveolar deposition. The modeling was then repeated for inhalation volumes and times selected to be more representative of typical smoking parameters. Volumes of 500, 1,000, and 1,500 mL and inhalation times of 0.5, 1, and 1.5 seconds were used and were intended to encompass the range of results obtained by Feng *et al.*,[10] who recently measured normal inhalation volumes and times during smoking at 1,081 $\pm$ 399 mL and 1.33 $\pm$ 0.52 seconds. Simplifying assumptions were made that the inspiration/exhalation speeds were constant and the exhalation time was the same as the inhalation time. (Since we are attempting only to show how differences in breathing patterns would change the deposition patterns, the results are still relevant.)

The literature on particle size and reasons why conventional particle deposition models do not appear to accurately predict cigarette smoke particulate deposition are reviewed. The complex issues, that govern both the size of particles generated when ventilated cigarettes are smoked and their subsequent deposition in the lungs are explored. Finally, the predictions of a recently published model for deposition of cigarette smoke are highlighted, to see how it might inform the debate about cancer type and deposition of CSP.

3. PART A: MATHEMATICAL MODELS OF PARTICLE DEPOSITION IN THE HUMAN LUNG

Models are developed to predict particle deposition in the lung for a variety of purposes: to investigate the implications of exposures to dust, radiation, ambient particles from industrial emissions, and to improve delivery of aerosolized pharmaceuticals. Existing mathematical models used to predict deposition in the lung are based on knowledge about the dimensions of the lung (lung morphology), characteristics of the particle including size and density, and the laws of physics. Since the first lung models were presented in 1950,[11,12] understanding of how best to represent the complex processes of airflow through the airways has been extensively refined. Yet, the results presented below have been remarkably consistent and convergent over a variety of modeling approaches.

3.1. Deposition in the Lung: A Function of Particle Size

Both experimental determinations and mathematical models indicate that particle deposition in the lung is strongly dependent on particle size. The largest

[1] Several researchers are critical of the ICRP's lung model, suggesting it may only be valid for a narrow set of parameters. However, the equations are publicly available and more straightforward to implement than other currently available models. The results presented here are intended to describe general trends and in this context, align well with other published data. The recommended deposition formula can be found in Chapter 5 of the ICRP66 publication.

particles (>2 μm in aerodynamic diameter[2]) deposit as a result of impaction, which occurs when the inertia of a particle causes it to deviate from the airstream, usually when direction of airflow in the lungs changes. Sedimentation affects particles 0.1 μm–2.5 μm in diameter, and occurs when gravitational forces cause the particle to "fall out" of a slowing airflow onto an airway wall. Particles <0.1 μm in diameter deposit as a result of random collisions with air molecules and eventually an airway wall, in a process called Brownian diffusion .[13]

To understand the physics of airflow and deposition, the lungs can be thought of as a series of sequentially branching "tubes," which become narrower and exponentially more numerous for each of 24 generations of branching. Air speed in the lungs is a function of the volume of air and the cross-sectional area of the tube it flows through. Because the lung widens from the trachea to encompass a cross-sectional area that fills the chest when the lungs are inflated, the velocity profile of the airflow through the lungs slows dramatically as it reaches the alveoli even though the individual airways are very narrow at this level of the lung.

"Total deposition" refers to the fraction of inhaled particles retained at any location in the lung, whereas "regional deposition" distinguishes the proportion of inhaled particles deposited in specific regions of the lung such as the tracheobronchial (TB) region and the alveolar (A) region. The typical predictions of mathematical models and experimental results for reference aerosols are illustrated by Fig. 1, which clearly illustrates the dependency of deposition on particle size. The figure is used here as an example of a modeling effort to show general trends apparent across a variety of modeling efforts. General patterns of deposition predicted by the sophisticated models now available are similar and correlate well with experimental data,[13–19] although small discrepancies still exist between modeling and experimental results.[20] Part A depicts total deposition efficiency and shows that not all particles, that are inhaled are deposited in the lung; many are exhaled. A minimum in deposition occurs at ~0.5 μm; particles in the size range of ~0.1–1 μm are subject to the least deposition overall because their size makes them large enough that the forces of momentum entrain them in the airflow, but not large enough to efficiently exit the flow by sedimentation or impaction.

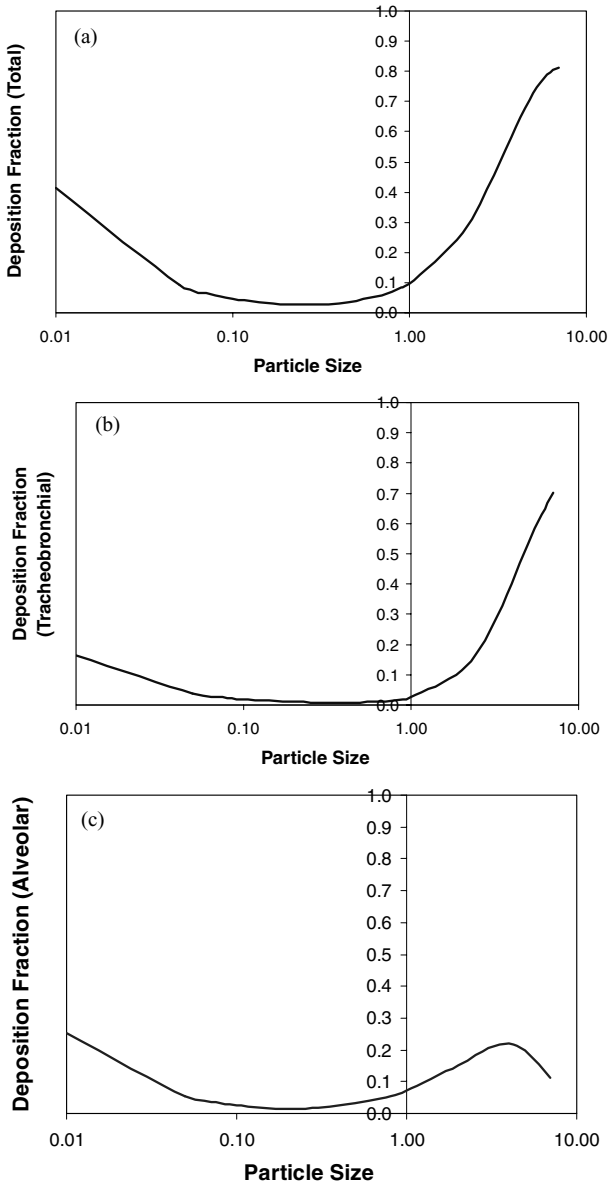

Fig. 1. Theoretically predicted particulate deposition using recommended deposition formulas from ICRP66[9] with a tidal volume of 1,000 mL and an inspiration speed of 250 mL/sec. Overall patterns of deposition are similar to those described by other modeling efforts using similar inhalation parameters (i.e., in[17]). The y-axis represents the fraction of particles entering the trachea that are deposited after a full breathing cycle. (A) total deposition; (B) tracheobronchial deposition; (C) alveolar deposition.

In the TB region (Fig. 1, part B), particles are likely to deposit most efficiently at diameters of ~1 μm or greater, and there is a strong monotonic relationship between size and deposition fraction. Sedimentation and diffusion dominate the deposition

[2] The term "aerodynamic diameter" refers to the diameter of a spherical unit density particle having the same terminal settling velocity as that of the particle in question. Throughout this article, the term "diameter" is used interchangeably with "aerodynamic diameter."

processes in the TB region. In the alveolar region (Fig. 1, part C), the pattern of deposition is more complex, and is a combined function of the likelihood that a particle will already have deposited in a larger airway and the efficiency with which it deposits in the alveoli. Because the alveoli have a large cross-sectional area, the flow of air drops to essentially zero. As a result, sedimentation is extremely efficient for particles that reach the alveoli. For particles in the 1–10 μm size range, deposition efficiency in the alveoli would theoretically increase monotonically with size. However, because deposition of the largest particles is so efficient in the tracheobronchial region, these particles typically do not reach the alveoli, and so the actual deposition fraction decreases as particle size increases beyond ~4 μm. The smallest particles do not have enough mass to deposit by sedimentation and deposition is governed by diffusion, a process that becomes more efficient as size of the particles decreases. Note that total deposition and alveolar deposition are similar for particles below about 1 μm in diameter, as deposition for these particles is governed by diffusion.

3.2. Deposition in the Lung: A Function of Ventilatory Parameters

Particle deposition also depends on breathing parameters, including inhalation volume (V), total time for the breathing cycle (t), inspiratory flow rate (Q), which is a function of V and t ($Q = V/t$), and breath-hold time (between inspiration and expiration). The ICRP model used to create Fig. 1 is a semiempirical model, which was developed for environmental dust exposures with radiation during sleep, regular breathing, and exercise. Other models, such as Risk Assessment Dosimetry Model[17] were developed for environmental particles from industrial pollution, or for purposes of controlled delivery of pharmaceuticals.[16] Depending on the purpose of the model, they may use inputs such as tidal volume (amount of air inspired during normal breathing) and forced vital capacity (amount of air that can be forced from the lungs after maximal inspiration).

The "breathing pattern" associated with smoking may be quite different. Smokers typically puff a small volume of highly concentrated smoke into the mouth, may hold it there briefly, and then follow with an inhalation of ambient air.[21] The inhalation phase is typically deeper than normal breathing; a recent review suggested that smokers inhale about 20–25% of their tidal volumes.[22] They may then hold the smoke in their lungs for a period of time before exhaling. The protocols devised by the FTC to determine cigarette yields are highly standardized (i.e., periodic puffing of 35 mL puffs over for two seconds every minute until a 2 cm butt length remains). However, the FTC protocols systematically underestimate smoking behavior in humans. In addition, there is considerable variability in smoking patterns across individuals, including among individuals smoking the same cigarette brand.[23,24] In a review of British American Tobbaco (BAT) studies on retention, Baker and Dixon refer to 1,969 measurements of inhalation depths ranging 600–1,600 mL, exhalation depths of 300–1,200 mL, and time held in lungs of 1–5 seconds.[25] Elsewhere, measured puff volumes were in the range of 21–93 mL, inhalation volumes ranged from 216 to 1,616 mL, and peak flow ranges for puffing were 28–99 mL/sec.[21,26] A recent effort by Philip Morris using a new technology called a Lifeshirt™[10] measured normal inhalation volume and time during smoking at 1,081 ± 399 mL, and 1.33 ± 0.52 seconds, and exhalation volume and time at 3,040 ± 959 mL and 6.39 ± 1.65 seconds.

Models and experimentation consistently indicate that slower inspiration speed and larger inhalation volume enhance deposition in the distal airways.[11,27,28] This is likely a result of increased residence time of particles, allowing increased opportunity for sedimentation and diffusion to occur. Increased inspiration speed may increase deposition efficiency for the larger particles in the upper airways,[16] where impaction is more likely to occur with the increased momentum created. Breath holding tends to increase deposition of particles at their furthest point of penetration due to increased chance for sedimentation to occur. For particles less than 1 μm, deposition would increase mainly in the alveoli.

The ICRP and other models we have cited were not developed for the specific case of cigarette smoke inhalation. It should be noted that the ICRP model used for the following figures is based in inspiration speeds associated with various levels of activity rather than one-time manipulations of a breathing cycle by an individual. However, they can still inform us about the types of systematic changes in particle deposition, that could be expected under various inhalation conditions. Figs. 2, 3, and 4 characterize the differences in deposition that would be expected for a range of particle sizes, and under several breathing pattern scenarios. The fraction deposited is based on the number of particles entering the trachea. Fig. 2 indicates that slower breathing without changing the volume of inhalation results in more alveolar deposition for particles greater than ~0.01 μm (due to increased impaction in the TB region). Fig. 3 indicates that

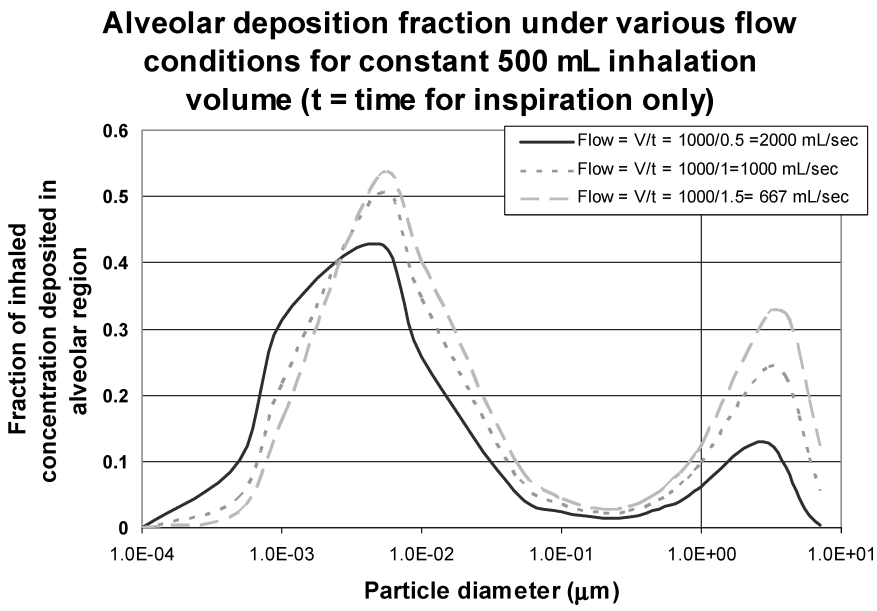

Fig. 2. Deposition fraction in the alveolar region increases slightly with slower breathing (inhalation volume held constant) for particle sizes greater than ~0.005 μm. Based on recommended deposition formulas in Chapter 5 of Annals of the ICRP.[9]

increased deposition in the alveolar region occurs with increased inhalation volume for most particle sizes, even if the breathing cycle time is maintained, and Fig. 4 indicates that combined longer, deeper breaths (while maintaining constant inspiration speed) increase alveolar deposition efficiency for most particle sizes.

These profiles align with other published efforts.[16,29] A mathematical model by Martonen indicates that breath holding between inspiration and expiration increases particle deposition in the alveolar region only, and that the increased deposition occurs for particles ~0.005–10 μm. His model also indicates that deposition efficiency in the tracheobronchial region is unaltered by breathing pattern for particles in the size range ~0.1–1 μm, which is the relevant particle size for CSP, as will be discussed next.

4. PART B: CIGARETTE SMOKE PARTICLES: SELECTING APPROPRIATE SIZE DISTRIBUTIONS

Despite extensive scientific efforts to determine the size characteristics of CSP, the dynamic characteristics of the aerosol combined with limitations of available methodology hinders consensus about the values

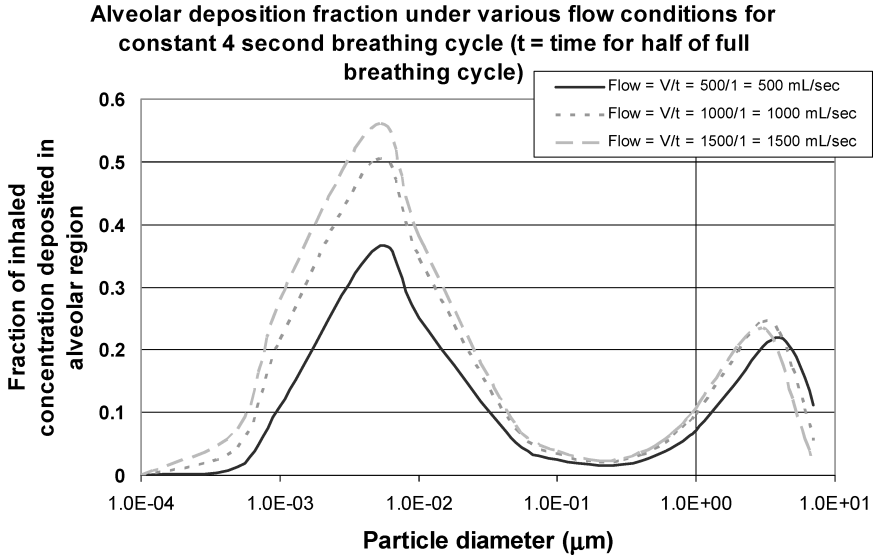

Fig. 3. Deposition fraction in the alveolar region increases with inhalation volume/inhalation speed (inhalation time held constant) for most particle sizes. Based on recommended deposition formulas in Chapter 5 of Annals of the ICRP[9].

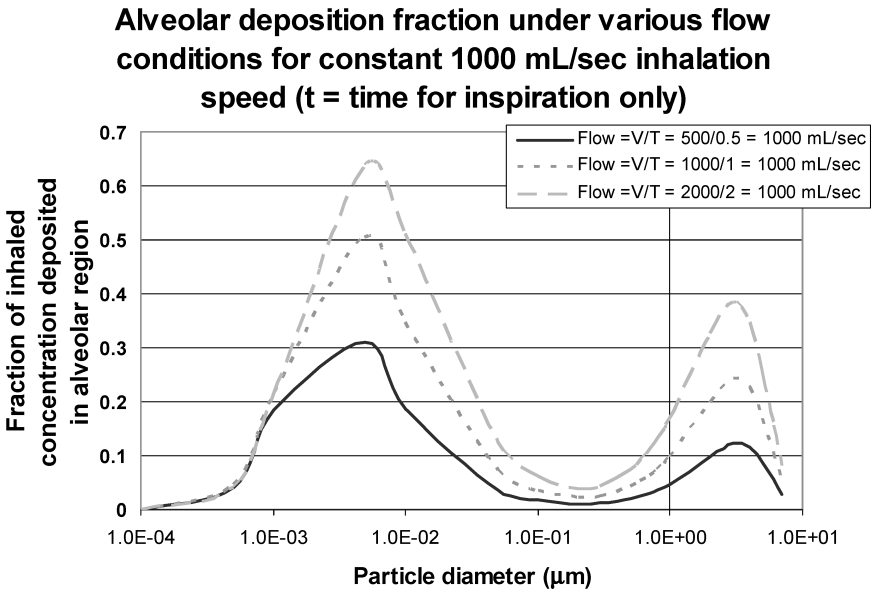

Fig. 4. Deposition fraction in the alveolar region increases with longer, deeper breaths that maintain the same airflow rate for particles greater than ~0.001 μm. Based on recommended deposition formulas in Chapter 5 of Annals of the ICRP.[9]

that best characterize CSP size distributions. Additionally, the type of reported value also varies, lending to the overall confusion: CM(A)D and MM(A)D[3] measured in various studies since 1950 range from 0.09 to 1.3 μm, and from 0.21 to 0.96 μm, respectively.[30–64] There is general consensus that the functional form of the size distribution is lognormal,[51] meaning that most of the particles formed are from the smaller end of the range of sizes produced. Where geometric standard deviations (GSDs) for CSP distributions were determined, they were all 2.0 or less, indicating a relatively narrow distribution. This suggests that most CSPs obtained from any specific sample have a similar size.

Ultimately, all estimates suggest that the diameter of CSP lies between ~0.1 and 1 μm. Many modelers (i.e.,[65]) use a count mean diameter of 0.2 μm as a central estimate. Based on Fig. 1, this is associated with virtually no deposition in the tracheobronchial region, and particle size at a minimum for deposition in the alveolar region. However, this does not jibe with the predominance of lung cancers observed in the tracheobronchial region. One reason is that some models do not account for carinal ridges in the bronchi, which may enhance deposition. As well, the alveolar surface area is very high. Cited values range from 80 m^2 (i.e.,[66]) to 140 m^2[9]—so even if numerous particles deposit there, they are not as concentrated. When the dose is normalized to surface area, the highest dose still occurs in the bronchial region.[67]

Even considering these issues, the mathematical models drastically underpredict total deposition for cigarette smoke when applied to reference particles in the CSP size range. Total retention of CSP has been measured at 96%,[68] at 70–90% for a five-second inhalation time, and at 94–99% for a 30-second inhalation time.[69] Baker and Dixon conclude in their review that most smoke retention values are within 74–99% and derive an average retention value of 88%.[25] Hinds found lower average total deposition in the range of 22–75%,[70] but the reported values were based on a limited number of subjects and were associated with large standard deviations. They have not been corroborated by any other results.

It turns out that CSP has some specific properties that may require special mathematical attention for accurate CSP lung deposition prediction.

4.1. Coagulation

The high concentration of fresh smoke (~10^9 particles per cm^3) promotes rapid coagulation[33,39,51,59,60] whereby particles in close proximity to each other aggregate into larger particles, resulting in fewer, larger particles. Most particle size determination efforts focus on characterizing the size distribution of fresh, unaged mainstream smoke,

[3] Count median (aerodynamic) diameter and mass median (aerodynamic) diameter. The benefits of using "aerodynamic" characterizations were not understood until relatively recently. As a result, some results do not account for the density of the particles. Note that because most of the mass is contributed by the larger particle despite their relative infrequency, it is always true that MM(A)D > CM(A)D.

and use rapid dilution of fresh smoke to prevent coagulation. Cigarette smoke comprises chemicals spanning a range of volatility, and the dilution promotes evaporation of the most volatile components, leading to smaller measured particle sizes.[59] *In vivo*, smoke particles will coagulate during the time for smoke to travel from cigarette to lung, so even accurate sizes determined for unaged smoke likely underpredict the size of CSP that reaches the lung tissue. Calculated coagulation constants[39,50,55,71] appear to be sufficient to move the mode of the size distribution from 0.2 μm to 0.25 μm, and the diameter of average mass from 0.29 to 0.5 μm,[1,72] a difference that is insufficient to account for the discrepancy between observed and predicted total lung deposition.

Coagulation effects are likely to be reduced as the bolus of smoke travels through the lung, and concentration of CSP is reduced due to particle deposition.

4.2. Hygroscopic Growth

The relative humidity of cigarette smoke is high (60–70%),[1] but the respiratory tract is an atmosphere of higher humidity (>99%), providing the opportunity for soluble particles to grow in size due to condensation. Various efforts predict growth factors of 1.3–1.7 for CSP in the respiratory tract,[61,63,73–75] with hygroscopic equilibrium reached in 0.001 seconds.[76] In general, hygroscopicity results in greater effective particle size, essentially shifting the predicted deposition fraction curves to the left.[77] According to Fig. 1, for a hypothetical initial particle size of 0.1 μm, hygroscopic growth might decrease total and alveolar deposition, while growth of a 1 μm particle would result in increased deposition.[78] However, an increase in size is accompanied by a decrease in density for many hygroscopic particles. This could mean that deposition may actually be increased only for particles of 1 μm or greater.[17]

A 1990 model of CSP accounting for hygroscopicity and coagulation effects predicted total deposition of 31–53% for particles of MMD = 0.27–0.52 μm under a breathing pattern intended to simulate smoking.[79] As with coagulation, hygroscopic growth does appear to affect deposition patterns in the lung, but together, they still appear unable to account for the discrepancy between observed and predicted total lung deposition.

4.3. Cloud Dynamics

If particle number density is high, particles may behave more like a single large particle than the collection of small particles they actually are: this is known as cloud dynamics and is the result of the surrounding gas traveling around rather than through a high concentration of particles. The larger effective diameter results in more efficient settling in the upper airways. Cloud behavior is favored when high number density parcels of particles are surrounded by relatively clear air. CSP may form such "packets" of particles, with large fluctuations in number density over time, and relatively narrow size distributions in each parcel.[64] Martonen predicted realistic CSP deposition patterns including at bifurcation hot spots by including coagulation, hygroscopicity, and cloud dynamics in his model.[80] The numerical results were compared to experimental findings: silicone casts replicating the lung were used in a smoking simulation and then cut open to determine where CSP had deposited.[81] Theoretical application of cloud dynamics for clouds of 10–20 μm predicted these deposition patterns as well as known patterns for cancer development, suggesting that this may be the dominant mechanism for the increased particle deposition in the lungs. A model by Broday, which incorporated hygroscopicity, coagulation, and cloud effects was also successful in predicting clinical, *in vivo*, and cast replica results, and predicted total, tracheobronchial, and pulmonary depositions of CSP at 78%, 66%, and 12% respectively.[82]

As with coagulation, cloud effects are likely to be reduced as the bolus of smoke travels through the lung, and concentration of CSP is reduced due to particle deposition.

It must be noted that although the models that account for coagulation, hygroscopicity, and cloud dynamics are probably better representations of the processes that occur within the lung (and may be more accurate) than models such as the ICRP model, they are still simplistic representations of a complex set of processes and are subject to large uncertainties.

5. PART C: COMPENSATION DURING SMOKING: HOW PUFFING AND INHALATION CHANGE

5.1. Smoking, Ventilation, and Compensatory Smoking

Assessing whether compensatory behavior could alter the deposition pattern of CSP in the lungs

requires knowing how smokers alter their behavior when smoking low-yield cigarettes. Ventilated cigarettes have small holes in the filter that allow clean air into the smokestream, diluting the concentration entering the smoker's mouth. However, smokers who switch to ventilated cigarettes may compensate for the lowered yield by blocking the ventilation holes with their lips or fingers, and by smoking more intensely.[4,21] Peer-reviewed studies found that compensation occurs mainly through increased puff volume with changes depending on the particular combinations of brands and high- or low-yield cigarettes being tested.[83–88] In general, smokers increase the volume of smoke drawn by as much as 40–50% when switching to a lower-yield brand, although this varies depending upon the brand. Increased numbers of puffs per cigarette were also measured in most studies, indicating increased total smoke inhaled. Puff duration typically remains fairly constant, so that the puff flow rate increases significantly. Several reviews of smoking compensation, including an independent review of industry documents, suggest that the most likely method of increasing smoking intensity is through increased puff volume and number of puffs taken.[2,6,89,90]

Puffing behavior is highly variable between individuals,[91] and also changes over the course of smoking a single cigarette. Typically, bigger, longer puffs are taken initially, with smaller, shorter puffs taken toward the end of the cigarette. The interpuff interval (time between puffs) tends to increase toward the end of the cigarette.[7,21,83] The way cigarettes are smoked over the course of a day may also change, with number of puffs decreasing with increased amount of previous smoking.[92] Nevertheless, compensatory changes in cigarette smoking appear to remain relatively stable within individuals over time.[26]

Data on whether smokers alter their inhalation pattern after puffing are sparse and contradictory. There appears to be some ambiguity about the meaning of "inhalation." Depth of inhalation properly refers to the maneuver executed by smokers after puffing to bring the smoke into their lungs; however, it is often used to describe the volume of smoke puffed. This ambiguity is reflected in the literature on compensatory smoking, in which "deeper inhalation" is often used to refer to increases in puff volumes.

Changes in inhalation depth were postulated in one study based on increased levels of expired CO and saliva thiocyanate, which could not be accounted for by other compensation methods,[93] and Hee showed that depth of inhalation was increased with decreasing cigarette yield in a small sample of smokers.[94] Others have been unable to measure any alterations in inhalation behavior.[86,95] A 2001 review of the controversy over compensation indicated that deeper inhalation with low-yield cigarettes was probable, although it had not been specifically adequately measured.[96] Several industry documents indicate interest in determining whether deeper inhalations and breath-hold times could increase nicotine dose to smokers,[97–100] suggesting that industry believes inhalation depth could be manipulated.

It is not clear whether increased puff volume due to compensation would be followed up by reduced inhaled volume in order to preserve total inhaled volume (puff + inhalation), or whether the postpuff inhalation volume remains static, such that total inhaled volume inhaled would change by the same amount as the puffed volume. The volume of the mouth and throat constrains the puff volume to a maximum of 100 mL;[91] whereas obtaining full compensation from some cigarettes would require larger puff volumes.[90] Puffing as an early portion of a continuous inhalation would allow complete compensation for highly ventilated cigarettes and is a plausible smoking maneuver. This would efficiently deliver smoke to the lungs as a bolus, similar to aerosolized drugs.

There also appears to be no information about the amount of time smokers of low-yield cigarettes hold the smoke in their lungs, although generalized references to increased breath-hold times[101] and the elasticity of breath-hold times can be found in the literature.[21]

6. PART D: DEPOSITION DEPENDS ON INTERACTION OF CSP SIZE AND COMPENSATION BEHAVIOR

6.1. Effect of Changed Breathing Patterns During Compensation

The preceding discussion indicates that models exist, that appear able to predict deposition patterns of CSP in the lung, but most are not publicly accessible. With the exception of the following model, they have not yet been used by their authors to investigate possible differences in deposition patterns according to the smoking pattern. Robinson and Yu[65] developed a model for CSP deposition, that accounts for coagulation, hygroscopicity, and cloud effects as well as simulating the breathing pattern of a smoker whereby a puff of smoke is initially drawn into the mouth, held there, and then diluted by clean air

Table I. Predicted Changes in CSP Deposition Fraction (Based on the Model Published by Robinson and Yu[65])

Increase In	Effect on Total Deposition Fraction
Puff volume from 25 mL to 75 mL	Negligible
Puff time	1.0% increase/sec
Inhalation time	2.8% increase/sec
Pause (breath-hold) time	1.9% increase/sec
Exhalation times	3.9% increase/sec

during inhalation. Their predictions for changes in deposition fraction according to smoking behavior are summarized in Table I.

The results describe only changes in total deposition and do not inform about which part of the lung is affected by changes. Table I suggests that if most compensation behavior truly affects only puff volume, the effect of changed breathing/smoking pattern on total deposition is likely to be negligible.

However, it seems probable that increased puff duration, depth of inhalation, (which would correlate with increased inhalation time), and breath holding are also associated with compensatory smoking behavior. The total time for just the inhalation phase can last from ~10 to 30 seconds,[21] suggesting considerable elasticity in the total amount of time a smoker might use for the entire smoking cycle. Robinson and Yu[65]'s results suggest that if smoking a ventilated cigarette systematically increases the time allotted to the various components of each smoking cycle, then the fraction of CSP deposited to the total lung will increase. According to the model summarized by Table I, if compensation extended each phase of the cycle (puff, inhalation, breath-hold, and exhalation) by just 0.5 seconds, the fraction of CSP deposited in the lung would increase by ~5% (summing the percentage of change that would be attributable to each phase). Figs. 2–4 indicate that for the relevant size ranges for CSP, increased inhalation time and breath-holding enhance deposition mainly in the alveolar region.

6.2. Effect of Changes in CSP During Compensation

Compounding the difficulty in assessing the diameter of CSP at various times after emission from the cigarette, CSP size is dynamic throughout the actual smoking process, and depends on the cigarette design, the puffing behavior of the smoker, and the length of the cigarette butt.[21] This makes it very difficult to adequately represent CSP size distributions for lung deposition modeling.

Ishizu[52] reported that larger puff volume decreased average smoke particle diameter. Chen[5,71] found that smaller puffs are associated with larger MMADs and that MMAD is likely to be larger when cigarettes produce a more highly concentrated aerosol. This suggests that most of the particles produced during smoking of ventilated cigarettes are smaller than for unventilated cigarettes. In 1977, Richardson of BAT found that ventilation reduced average particulate sizes by reducing water uptake,[102] but in a 2004 review on behalf of Philip Morris USA, Bernstein concluded that the particles did not appreciably change in size with ventilation.[22] In 1986, RJR described how CSP size fluctuated over the course of a puff, with the number mean diameter in the range of 0.3–0.4 μm (depending on the conditions) within the first half-second, dropping quickly to a diameter of about 0.2 μm, and then steadily increasing toward the end of a two-second puff.[103] Increased ventilation of cigarettes appeared to raise the minimum particle size observed, but extend the period of time during which the particle size was at a minimum. In general, most of the particles generated were from distributions with MMAD between 0.25 and 0.35 μm.

Because CSP size is dynamic, the actual amount of CSP that penetrates to each region of the lung is unclear. To facilitate the discussion of how compensatory changes in inhalation/breathing/smoking patterns might affect the deposition pattern, we use the term "*effective particle diameter*": the reference diameter that best represents an observed deposition pattern throughout the lungs. Because CSP appears to grow in the respiratory tract, the effective particle diameter for any particle would be larger than the initial particle size emitted from the cigarette. Figs. 2–4 suggest that decreasing flow by increasing inhalation time consistently enhances alveolar deposition for any effective diameter of ~0.005 μm or greater, and increasing flow by increasing inhaled volume only, or maintaining flow for deeper, longer inhalations (and exhalations) consistently enhances alveolar deposition for any effective diameter of ~0.001 μm or greater. The extent of the change in alveolar deposition depends on the specific effective particle diameter.

Predictions from lung deposition models are representations of mathematical equations and should be taken as estimates rather than precise values. Fig. 5 suggests that if the effective particle diameter was actually 0.2 μm, increasing the depth and length of

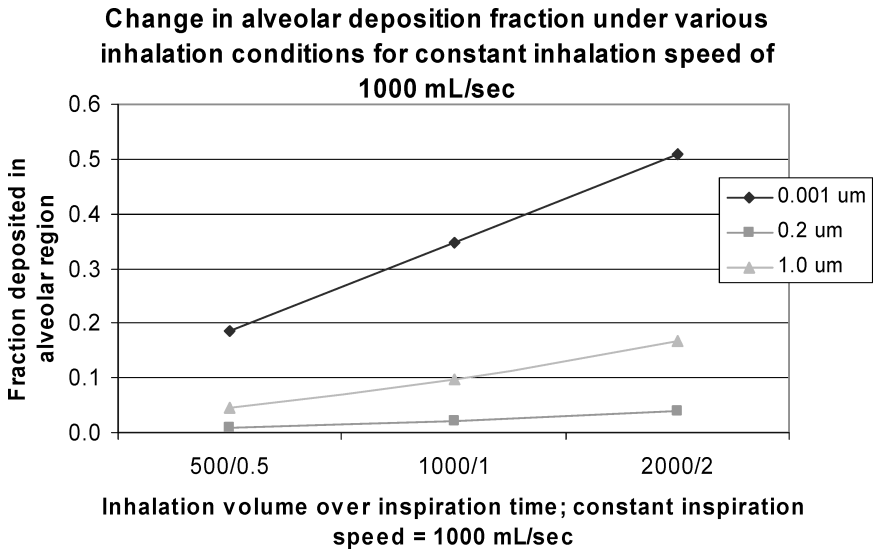

Fig. 5. Change in alveolar deposition for three particle sizes as breathing becomes deeper and longer (inspiration rate is maintained). Based on recommended deposition formulas in Chapter 5 of Annals of the ICRP.[9]

inhalation by a factor of 4 would alter the predicted alveolar deposition fraction of the particles by ~3%. However, if the effective particle diameter is 1 μm, the same change in ventilatory parameters results in a ~15% change in predicted deposition fraction. If the effective particle diameter was very small, say 0.001 μm, the change in deposition fraction might reach ~30%. Realistically, the specific percentage changes are uncertain—and different sets of inhalation parameters might alter the predicted fractional deposition; however, the overall pattern demonstrates the importance of understanding how particle size changes inside the lung.

6.3. Absolute Amount of CSP Deposited

Actual deposition (dose to lung) is a function of the concentration and size of delivered CSP as well as the depth and speed of inhalation—all of which may depend on the degree of cigarette ventilation (see Fig. 6).

Increased deposition efficiency of cigarette smoke to a particular region is insufficient to suggest that compensation could cause a shift in location of smoking-related cancer. It is more important to assess whether a change in *absolute amount deposited/dose* to a particular region occurs. Ventilated cigarettes ostensibly reduce the particle concentration delivered to the smoker. The extent of dilution depends on proximity of vents to filter tip, number of vents, and vent size,[104] and can reach 90% for some cigarettes in smoking-machine tests.[105] In reality, many smokers partially block the vents while smoking, reducing the level of dilution below theoretical levels. As well, puffing with increased velocity reduced filter effectiveness, allowing more highly concentrated smoke to reach the smoker.[6]

The behavior of compensation creates a complex interaction between altered smoke concentration and altered puffing/ventilation, both of which determine the absolute amount of particles delivered to each region of the lung. The absolute dose per cigarette to

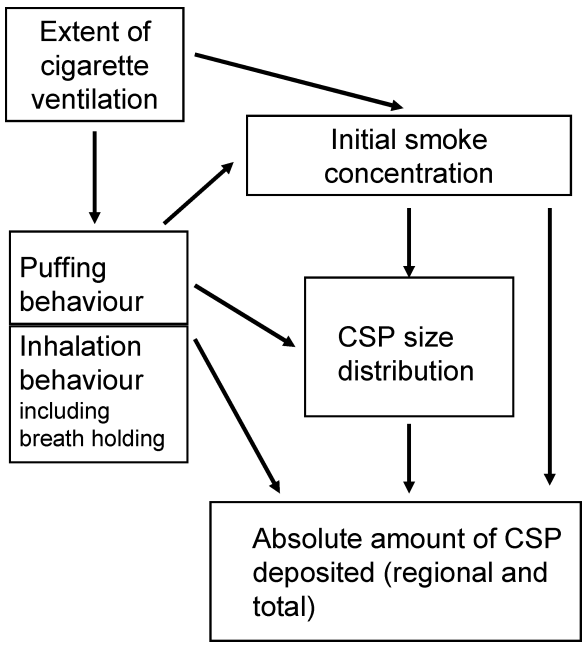

Fig. 6. Factors affecting how much CSP deposits in each region of the lung.

any part of the lung thus depends on initial smoke concentration and intensity of puffing (both of which determine the effective particle diameter), volume of smoke puffed, the number of times the cigarette is puffed, the depth and speed of inhalation, breath-hold time, and speed and volume of exhalation. Because the size range considered appropriate for CSP ($\sim$0.1–1 μm) is centered over a minimum in deposition efficiency, predicting a difference in particle size between two conditions is insufficient to determine whether deposition might increase or decrease; knowing the actual sizes involved for each scenario is crucial. However, with ventilation appearing to reduce average particle sizes, and processes in the respiratory tract causing particle growth, it is difficult to identify an appropriate effective particle diameter.

7. CONCLUSIONS

The literature is not mature enough, nor are the deposition models that adequately describe CSP activity in the respiratory tract accessible enough to allow accurate and precise prediction of CSP deposition resulting from specific patterns of ventilation. Given the uncertainties about initial and effective particle size, magnitude of smoking behavior changes, and the difficulties of precisely quantifying the small changes in deposition fraction that would be observed in the size range generally associated with CSP, it is impossible to determine whether compensation could sufficiently alter patterns of CSP deposition in the lung to elicit a shift in lung cancer sites. If effective particle sizes and inhalation, puff duration, and/or breath-hold times were known and found to be consistently different between two types of cigarette design (i.e., high and low yield), systematic changes in deposition patterns are plausible. However, careful analysis of the interaction between altered initial CSP concentration and altered regional deposition fraction would be required to determine if a difference in absolute dose would be predicted.

Even if further research reveals that the absolute change in alveolar deposition of CSP that results from compensatory smoking at the cigarette level is small, deposition from relatively more puffs on many cigarettes coupled with the relatively slower clearance of particles from the alveolar region[106] may result in an important increase in dose to the alveoli over the long term. Overall lung deposition is typically higher in patients with chronic obstructive pulmonary diseases such as chronic bronchitis,[29] which is common among long-term smokers, potentially magnifying the problem. The small particles that reach the alveoli have a relatively much larger surface area than their larger counterparts, and are thus potentially capable of bringing large quantities of adsorbed gases into contact with the tissues of the distal lung.

Mathematical models are only representations of reality and are subject to many limitations. Many of the available mathematical deposition models assume a uniform concentration of particles being inhaled. In smoking, the smoke is typically inhaled first and is likely to penetrate deepest into the lung and remain in the lung the longest of all the inhaled air. Research on pharmaceuticals delivered by aerosols (such as bronchodilators used in asthma) indicates that mathematical models perform relatively well for bolus delivery.[29] However, pharmaceuticals, unlike cigarette smoke, are not held in the mouth before inhalation, a practice that could result in a substantial amount of CSP deposition in the mouth before inhalation, altering the concentration entering the trachea. While Robinson and Yu's model accounts for mouth deposition, it is only one model and its results require confirmation from other modeling groups.

Most models are deterministic in nature, estimating deposition for some "reference person." Modeling and experimentation indicate that interindividual variability in lung morphology and breathing behavior significantly affects deposition patterns,[20,107] although deposition data do not appear to correlate well to significant spirometric parameters such as total lung volume or lung capacity.[12,108] Recently, stochastic models have begun to explore the implications of interindividual variability in lung morphology/anatomy and breathing patterns for particle deposition. Future research should consider that interindividual variability may easily overwhelm small changes in smoking behavior that occur with compensation, obscuring the impact of compensatory smoking on deposition patterns for any population.

Unfortunately, mathematical lung model predictions are rarely presented alongside estimations of confidence limits. Whether the potential differences in deposition fraction are large enough to be of importance in the face of model uncertainty is not known. Useful models for predicting CSP deposition patterns, which account for effects of coagulation, hygroscopicity, and cloud effects appear to be under development by several research groups.

Perhaps the observed shift in cancer sites is related to chemical changes in CSP during intense smoking rather than smoking pattern itself: it has also been shown that the increased intensity of smoking

observed with compensation may preferentially increase NNK (typically related to adenocarcinoma) relative to B[a]P (more often related to small-cell carcinoma), which may explain shift in cancer sites.[85,109] This is a particular concern since it may be coupled to a decrease in particle size and therefore more efficient delivery to the alveoli.

Future research should continue to separately address (i) whether consistent compensation behavior exists that could plausibly alter dose of CSP to any region of the lung for any particle size that could represent CSP. This should include an investigation of inhalation depth and breath holding, and (ii) what the range of initial possible CSP sizes is under real smoking conditions (including when compensation is occurring) for a range of cigarette types and yields. A model designed to predict CSP uptake from different types of cigarettes to various lung regions over the long term might provide insight.

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