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Aerosol Deposition in the Upper Airways of a Child

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ABSTRACT

In a small child, normally only a small amount of inhaled aerosol particles reaches the lungs because the majority deposits in the upper airways. In this study, the upper airways of a 9-month-old child, based on computed tomography (CT) data, are modeled to serve as input for a computational fluid dynamics package (CFX). Verification of the validity of aerosol deposition calculations by this package is accomplished by evaluating two test cases, which also can be solved analytically. The numerically found sedimentation fraction in a horizontally placed straight pipe shows deviations from the exact solution for small particle sizes (less than 3 micron) due to small velocities generated by the use of an unstructured mesh. Although these velocities are small compared to the mainstream velocity, they are comparable with the terminal settling velocity of such a particle. Also the test case for inertial impaction in a bend pipe demonstrated the same problem. With this in mind, the aerosol deposition of 3.7-micron particles in the upper airway model of the child (SAINT-model) was calculated. Results were compared with experimentally found results in the literature. For small tidal volumes and flow rates, the computational results matched the experimentally measured results. However, large deviations were found for higher flow rates and small particle sizes. Most probably the incompletely modeled entrance at the nose and inertial effects due to turbulence might be responsible.

Key words: upper airway deposition, mathematical modelling, children, aerosols

INTRODUCTION

Several techniques are applicable to the administration of drugs in the correct part of the human body. For lung diseases, drug delivery via the inhaled route has been used for the past 50 years. This method is preferred over oral drug delivery because the drug will be targeted directly to its site of action. This results in an immediate effect of the drug and a lower necessary dose. Several deposition models in literature show that the upper airways act as a trap for the drugs, which results in the drugs being swallowed.[1,2] This can lead to unpleasant side effects of the drugs. The aim of all studies concerning drug delivery through inhalation is to improve the quality of aerosol therapy. It appears to be very difficult to deliver drugs into the lungs of young children. Studies have shown that, for an adult, about 50% of the applied drug

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reaches the lung, whereas for a child this percentage is less than 10%.[3] To find the explanation for this, it is essential to be able to understand the mechanisms of aerosol deposition. Furthermore, the difficulties of handling children should be taken into account. Cooperation, breathing pattern, nose breathing, and the size of the airways create differences in the effectiveness of drug inhalation between a child and an adult. For practical as well as for ethical reasons, it is difficult to perform *in vivo* studies in children. The Sophia Children's Hospital in Rotterdam started a study on a physical model of the upper airways (nose and throat, with a closed mouth) of a 9-month-old girl.[4] The model was made on the basis of computed tomography (CT) scans, of which the data were converted into computer-aided design (CAD) data that define the three-dimensional (3D) geometry. Through these data, a physical model was made by stereolithography. This method created a physical model (SAINT-model) that is a reconstruction of the exact geometry of the upper airways of this child. The results of the *in vitro* measurements gave a realistic estimation of the behavior of aerosolized drugs in the upper airways of this child. It is time and money consuming to predict the behavior of aerosol deposition in each individual young child by the use of a physical model. We therefore tried to predict the behavior of aerosol deposition in the upper airways of a child by computerized simulations with a commercial computational fluid dynamics (CFD) program named CFX®.

METHODS

Verification of the computational method

Case 1. Sedimentation. To verify the validity of the calculations made by this program, two test cases are investigated. To analyze aerosol deposition by sedimentation, a horizontally placed straight pipe with a parabolic (Poiseuille) profile is investigated. For this case, an exact analytical solution exists. According to the manual of CFX,[5] the particle transport model evaluates all forces acting on a particle. The equation of motion for a particle is derived by Basset, Boussinesq, and Oseen for a rotating reference frame. For a non-rotating reference frame and for particles (like water) with a higher density than its surrounding fluid (air), this equation can be reduced to:

$$m_p \frac{d\vec{v}_p}{dt} = \frac{1}{8}\pi\rho_f d_p^2 C_D|\vec{v}_f - \vec{v}_p|(\vec{v}_f - \vec{v}_p) + \vec{F}_b$$

where m_p is the mass of the particle, d_p the diameter, v_p is its velocity, ρ_f is the density of the fluid, v_f is the velocity of the fluid F_b is the force of gravity, and C_D denotes the drag coefficient. Implementation of particle transport in CFX-5 can be described as a multiphase flow in which the particles are modeled with an Eulerian description, whereas the dispersed phase uses the Lagrangian transport model. The application of Lagrangian particle tracking involves the integration of the path of the particles through the discretized domain. The particle displacement is calculated using forward Euler integration of the particle velocity over time step, delta t. The set of equations solved for the surrounding fluid consists of the unsteady Reynolds-averaged Navier-Stokes equations in their conservation form.

The interior of the straight pipe is discretized into a fine mesh to obtain accurate results in the simulation. Although a simple shape such as a cylindrical domain can be meshed in a structured way using hexahedral elements, the straight pipe is meshed using an unstructured mesh, with tetrahedral elements. The reason for this is that the complex geometry of the upper airways of a child cannot be meshed properly by employing a structured mesh. Therefore, an unstructured mesh with tetrahedral elements will be used later on for the SAINT-model. In this investigation, an inflation layer is used for resolving boundary layers in the near wall regions to capture viscous flow. Inflated layers consist of an accumulation of prismatic elements. This results in a computationally more efficient mesh near the boundaries of the geometry, where velocity gradients are large in the direction perpendicular to the surface, but small parallel to it. To obtain a mesh-independent solution, the straight pipe is divided into 407,602 elements (321,902 tetrahedrons and 85,700 prisms). An impression of the mesh is shown in Figure 1.

To be able to make a useful comparison between analytical results and the results from CFX, all input values were chosen equal. Air at 25°C ($\mu = 1.84 \cdot 10^{-5}$ kg/msec) is used as the fluid, while the density for the particles is chosen as 998 kg/m^3, the same as water. The length of the pipe

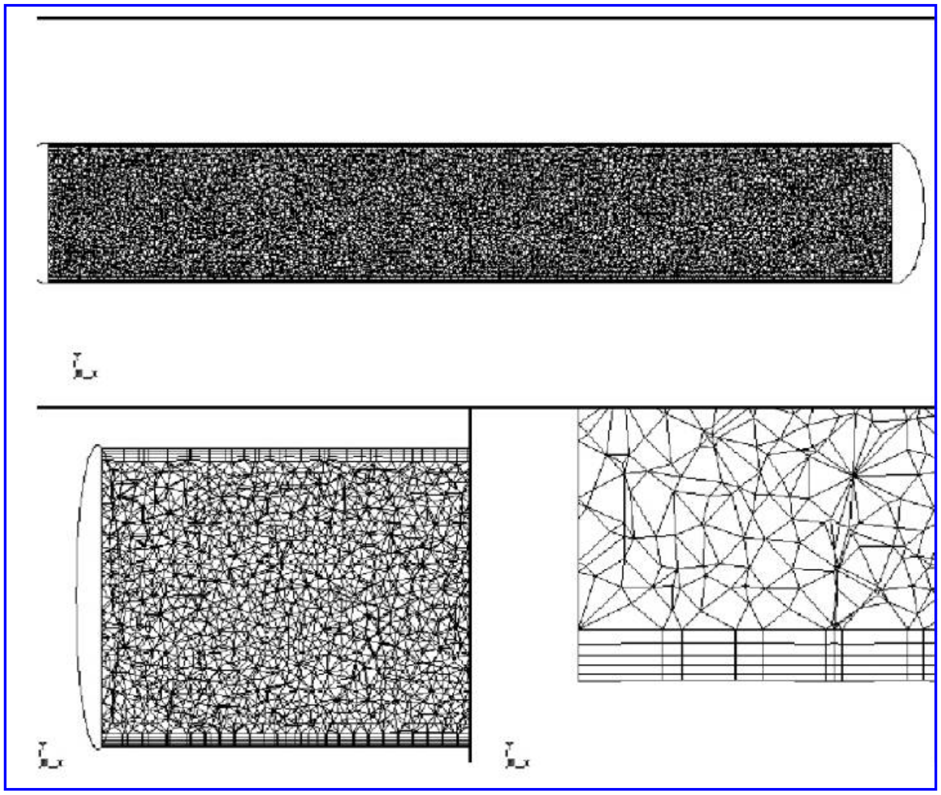

FIG. 1. Cross-section of the tetrahedral/prismatic unstructured mesh.

was 0.03 m, and its diameter was 0.005 m. It should be noted that in CFX the particles are "one-way coupled," which means that the particles do not influence the continuous-phase flow. A more advanced method would be the "fully coupled" method, where exchange of momentum between the continuous phase and the disperse phase takes place. As the analytical solution is obtained from the non-coupled model as well, the "one-way coupling" is used for the CFX simulations. When the results of the CFX simulation are compared to the analytical results, a considerable difference is observed.

Figure 2 presents the results of CFX as well as the analytical results. Deposition is less for the higher velocities; particles will not have the time to deposit before they reach the end of the tube. The deposition is also less for smaller particle sizes. For all situations, the CFX solution gives a lower deposition percentage. For large particles, this difference is relatively small. Between the analytical result and the CFX result, there is a maximum difference of 10%. But for the small particles of 1 μm, the difference is unacceptably large. The cause of the deviation of the results of CFX can be identified as the error that the numerical method makes in calculating the velocity of the surrounding fluid compared to the prescribed Poiseuille profile used for the analytical solution. Poiseuille flow is an exact solution for steady, fully developed laminar flow in a straight pipe. Discretization of the domain results in a disturbance of the flow. Infinitely small elements in combination with a convergence of the simulation will result in the exact Poiseuille flow.

The L_2-norm of the velocity, which gives a norm of the error, can be determined for each component of the velocity. The dimensionless L_2-norm is defined as:

$$L_2 = \sqrt{\frac{1}{n}\sum_{i=1}^{n}\frac{(v(x_i,y_i,z_i) - v_{theory}(x_i,y_i,z_i))^2}{\bar{V}_x^2}}$$

At an average velocity of 1.27 m/sec, the L_2-norm of the velocity component in the x-direction is in the order of 10^{-2}, which can be interpreted as a accuracy of about 1%. For the velocity in the y-direction, the L_2-norm is in the order of 10^{-4}. When compared to the terminal velocity of the particles, this can be interpreted as not being very accurate since the terminal settling velocity of a particle of 1 μm is $3.0 \cdot 10^{-5}$ m/sec. This implies that small particles will predominantly follow the

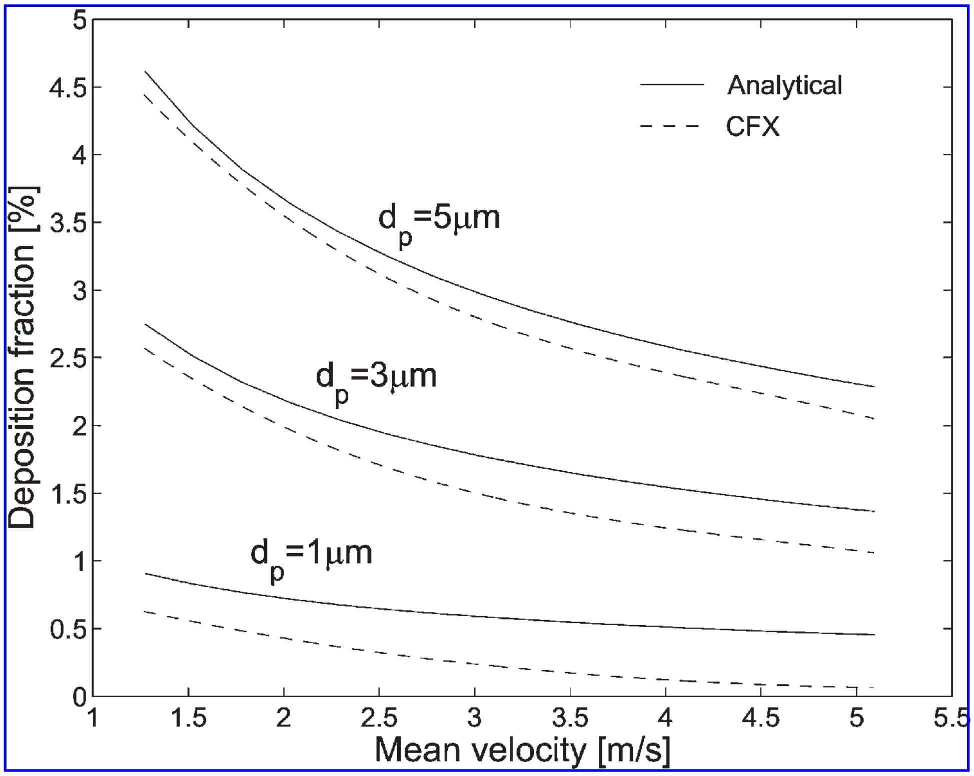

FIG. 2. Comparison of results of the analytical solution and the CFX simulation.

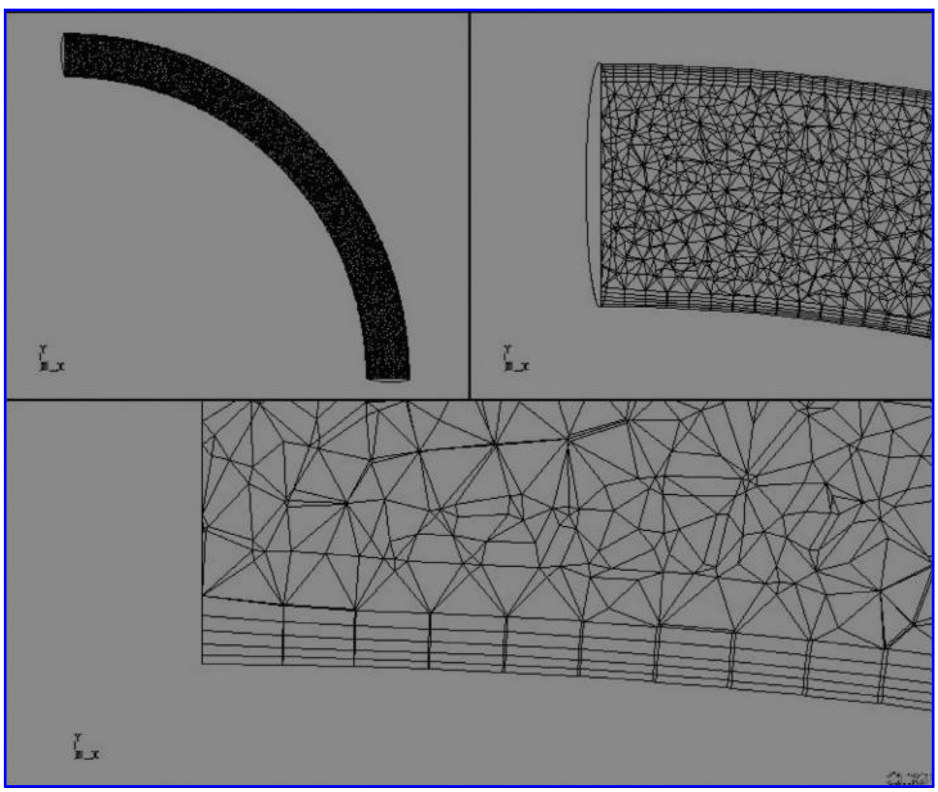

FIG. 3. The mesh of the bend pipe.

fluid (i.e., the terminal settling velocity will not have any substantial effect), and therefore, the particle will not drop steadily. Using a structured mesh, this problem disappeared, and the difference between the analytical and numerical solution became negligible. However, the upper airways of a child will not allow the use of a structured mesh, so calculations for gravitational deposition rates of particles less than 3 micron should be critically evaluated, since large deviations from reality might occur.

Case 2. Inertial impaction. To verify the deposition by inertial impaction for CFX, a bend pipe with a plug velocity profile is investigated. The outer radius of the pipe was 0.02 m, while its diameter was 0.0025 m (Fig. 3). The analysis of the particle deposition in the bent pipe results in the dashed lines in Figure 4. The results from CFX for the deposition fraction are higher than the analytically found values. This can be attributed to the deviation of the flow from the plug flow. The physical properties are modeled correctly, as indicated by the similarity between the characteristics of the results from CFX and the analytical solution; the relation between velocity and deposition fraction is linear, and the deposition fraction increases with increasing velocity. For large particles, the difference is low (with a maximum of 5%). But for small particles of 1 μm, for which the deposition fraction is small, the difference is high.

Upper airway model

To be able to make a reliable comparison between CFX results and experimental results, two issues must be addressed. First, the physical model used for the experiments must be equal to the CAD model used for the CFX simulations. Second, all input values for CFX must resemble the conditions under which the experiments have been carried out. For this research, the airways of the SAINT-model used by Sophia Children's Hospital in Rotterdam[4] are reconstructed. The data of the original SAINT-model used by Sophia Children's Hospital in Rotterdam for the experiments were given in a STL-file. This is a type of file that contains data in the form of a closed triangulated surface mesh, surrounding a volume. The STL-file was used for building the physical model by stereolithography. This physical model consists of a part of the head of a young child

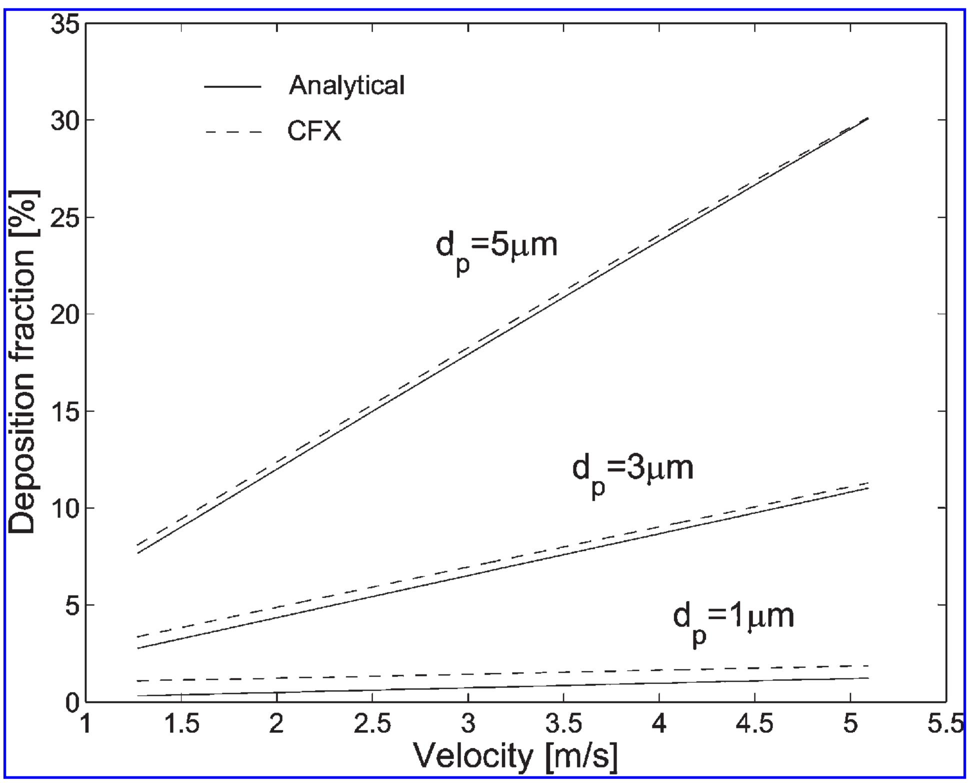

FIG. 4. Comparison of results of the analytical solution and the CFX simulation.

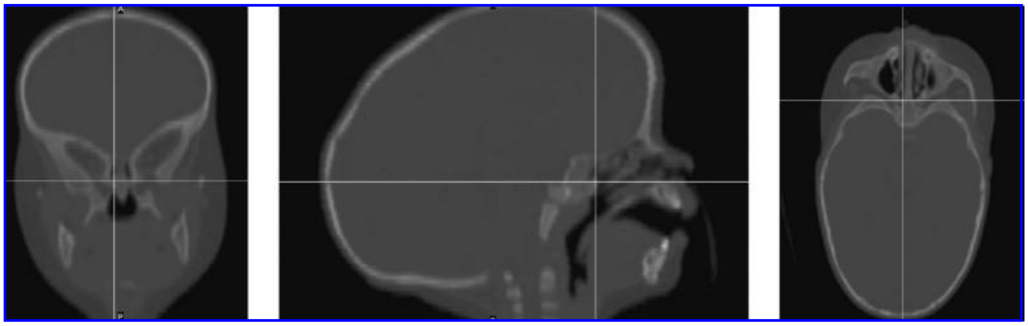

FIG. 5. CT-scan data of a 9-month-old child breathing through her nose.

with the upper airways as a cavity within this solid body (Figs. 5–8). The cavity of the mouth is not connected to the trachea in this model. In other words, the child was solely breathing through the nose, and although the mouth was opened, there was no connection with the airflow passing from nose to lungs.

For the CFD model, the computational domain is formed by the upper airways, which are the cavities in the cast of the child's head—i.e., not the solid parts of the SAINT-model. The original CT scan of the young child is a 3D scan built from 2-mm slices.[4] The images of this CT scan are edited by the software package MIMICS® (Materialise's Interactive Medical Image Control System, Leuven, Belgium). This program converted the 3D CT scan into a 3D image (Fig. 5) viewed from three mutually orthogonal directions.

The conversion from CAD to an appropriate mesh for CFX is carried out in three steps. The STL file is converted into a solid body, which was exported as an appropriate file for a mesh program. After that the result is discretized into a good quality mesh. The mesh program used for importing the STL-file was ICEM CFD. Because this program imports STL as a geometry with a single surface, this surface was split to mark the inlet (the nostrils) and the outlet. The third step, discretizing the computational domain, resulted in the base mesh was 331,287 tetrahedral elements.

The experiments were done by simulating real breathing of a young child using a breathing simulator. This sinusoidal breathing pattern has the following settings:

1. Respiratory duty cycle (inspiratory time (Ti)/total respiratory time ($Ttot$) = 0.42:1
2. Influence of tidal volume (TV) is tested with TV's of 25, 50, 75, 100, 150, and 200 mL with a fixed respiratory rate (RR) of 30 breaths/min. Taking the settings into account, the breathing pattern can be described as two sinusoidal parts. Because this breathing pattern consists of two separate parts, with a non-continuously differentiable point at $t = 0.84$ ($= Ti$), this pattern cannot be imported into CFX as a single equation. Therefore, the breathing pattern has been approximated with a 6th-degree polynomial.

The most important difference in the simulations of the straight and the curved tube is that some boundary conditions are time dependent and, thus, the simulation becomes transient. The

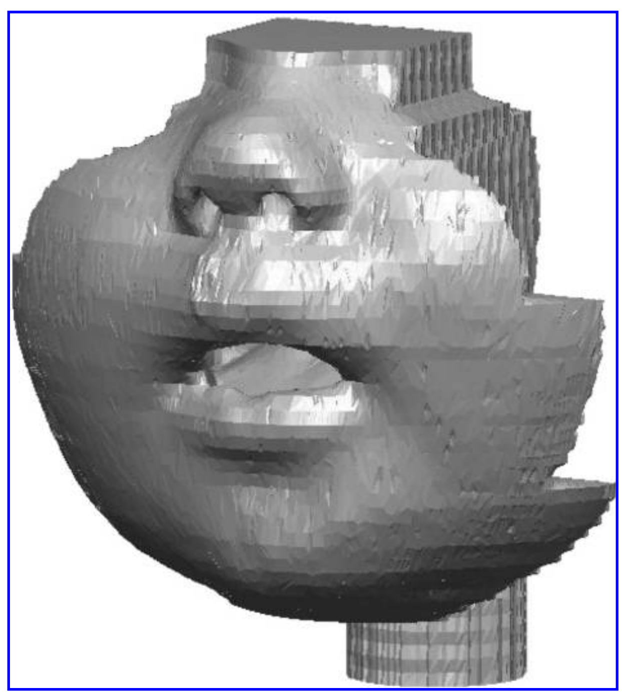

FIG. 6. Stereolithographic model reconstructed from the CD scan data.

FIG. 7. Polylines of upper airways by MIMICS®.

breathing pattern is time dependent, and more particles will enter the domain when the flow speed is high, so the mass flow rate of the particles is also time dependent. For exhalation, the mass flow rate of particles that are added to the domain becomes zero.

CFX-5.7 has been used for transient particle tracing. To be able to give the entering particles the same velocity as the surrounding fluid, the volume rate of the surrounding fluid must be converted into a velocity by using the total area of the inlet.

The number of inserted particles per second is a required transient input value for the inlet. The particle diameter distribution can be set in the boundary conditions of the inlet. For this research, the mass median aerodynamic diameter (MMAD) of the particles budesonide pMDI (Pulmicort R® 200 μg) is 3.7 μm. The minimum diameter of the particles is set to 1 μm, and the maximum to 5 μm. The geometric standard deviation (GSD) is assumed to be 1.4, in accordance with the aerosol deposition measurements of the lung dose.[4]

RESULTS

A typical velocity field at mid-inspiration (the curve in the inset depicts the volume flow rate) can be seen in Figure 9, while Figure 10 shows some particle trajectories.

At first, the simulation is set up to simulate a complete breath of 2 sec. This means that inhalation as well as exhalation is simulated in one simulation. For a complex geometry, it is to be expected that the flow will be turbulent. However, turbulence models in CFD programs are not suitable for modeling aerosol deposition in complex geometries of the throat.[6] Since turbulence effects are limited due to the small sizes of the geometry, modeling the flow as a laminar flow is acceptable for low velocities, i.e., $TV = 25–150$ ml (Reynolds' number stays low: $RE < 1000$). Turbulence occurs for high velocities ($TV \geq 200$ ml), that is, a high Reynolds' Number ($RE > 1000$).

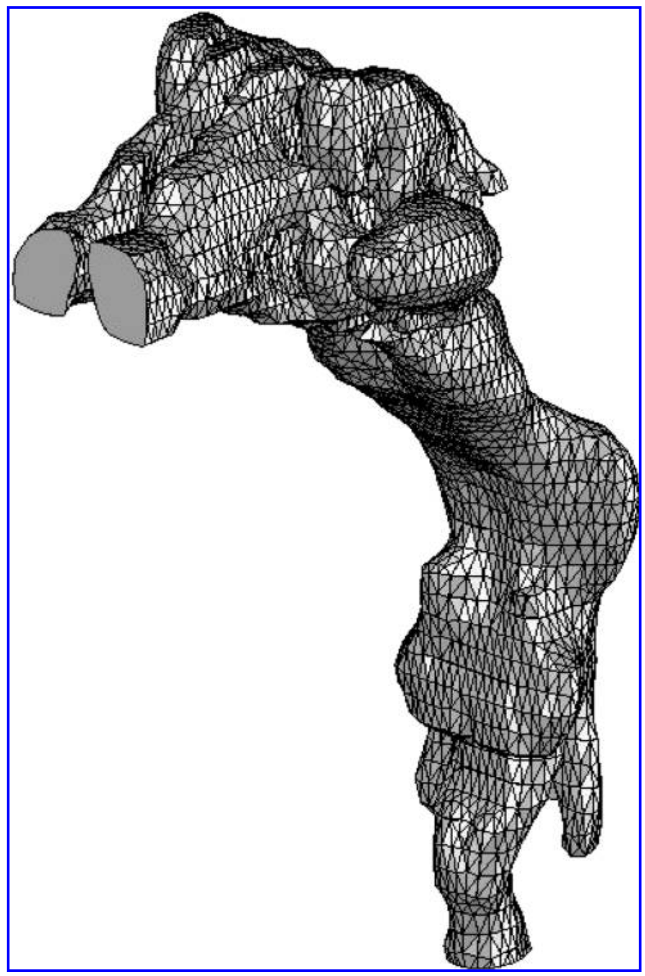

FIG. 8. Mesh of the upper airway model.

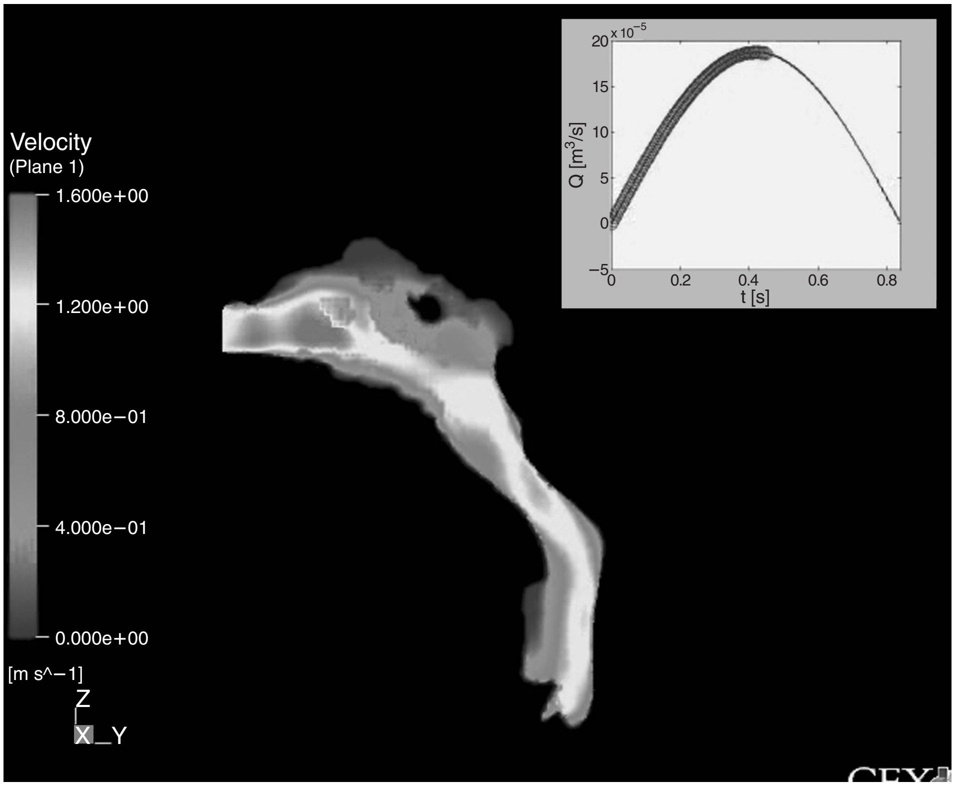

FIG. 9. Flow velocity in the upper airway model about halfway through inspiration.

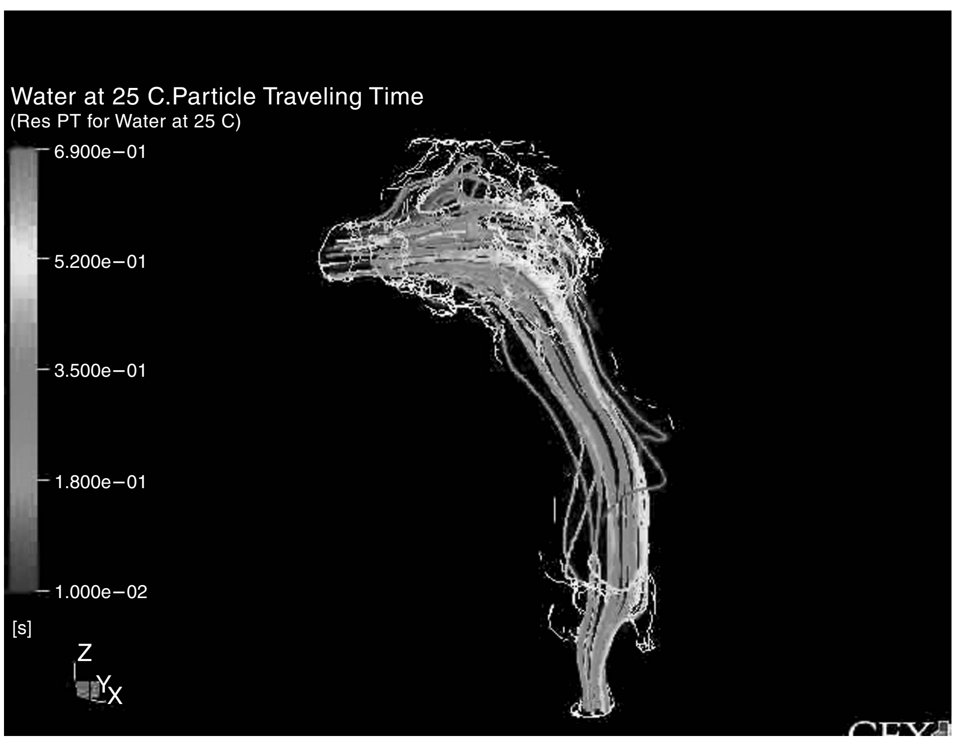

FIG. 10. Particle trajectories.

The particles statistics can be split into three parts: particles that hit the wall, particles that did not leave the domain (and did not hit the wall), and particles that left the domain through the outlet. The particles of the second category entered the domain through the inlet shortly before exhalation, and thus at the moment of exhalation these particles did not have the chance to reach the outlet. In reality, these particles will partly deposit in the upper airways during exhalation, while the rest will be exhaled. It can be concluded that none of these particles will reach the lungs.

Figure 11 shows the deposition percentage of all categories for the specified range of tidal volumes (25–200 ml). The small increase of deposition percentage of particles that hit the wall with a higher tidal volume (and thus a higher flow velocity) can be attributed to the effect of inertial impaction. Sedimentation plays a minor role in the simulation, since the gravity acts in the direction parallel to the largest part of the airways. The average traveling time of a particle to get from the inlet to the outlet at the end of the inhalation is 0.25 sec for a TV of 25 mL which is about 30% of the total inhalation time. Particles entering during the last 0.25 sec of the inhalation therefore will not reach the outlet and will stay in the domain. For higher TV's, this traveling time decreases to 0.1 sec (about 10% of the inhalation time), resulting in a lower percentage of remaining particles. Therefore, the decrease of remaining particles can be attributed to the low-flow velocity at low tidal volumes, compared to the high-flow velocity at high tidal volumes. Aerosol deposition can be analyzed also by considering the location where most aerosols deposit.

As can be expected, most particles deposit at locations where flow accelerates the most by changing direction. Figures 12 and 13 show that most particles are deposited at two specific locations. The first deposition location is close to the nostrils, where flow splits into different directions into the paranasal sinuses. The second location is at the larynx, where the flow has to make a sharp turn.

The experimental results of the deposition in the SAINT-model are presented as a percentage of the nominal dose that is deposited onto the wall. The nominal dose is the dose that is mentioned on the label of the drug, so this is a fixed value. The output of CFX will be presented as a percentage of the total amount of particles entering the domain. Because the domain in CFX is limited to the SAINT-model, without the spacer and the face mask that were present during the experiments, the deposition percentage of the experiments must be converted to the appropriate values. Literature on the experiments[4] present the found values for the deposition at all loca-

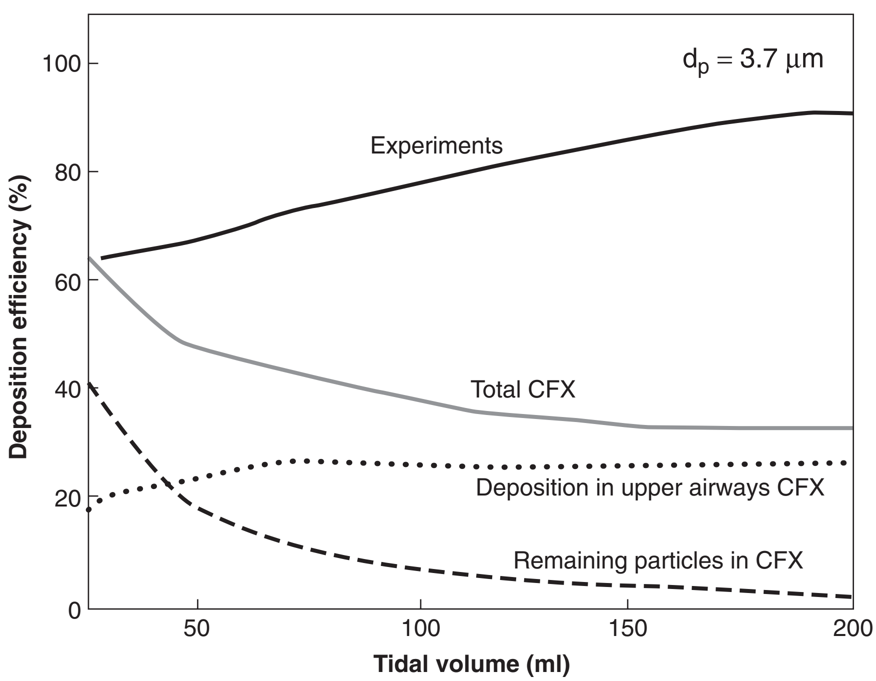

FIG. 11. Comparison of deposition results of experiments and CFX simulations.

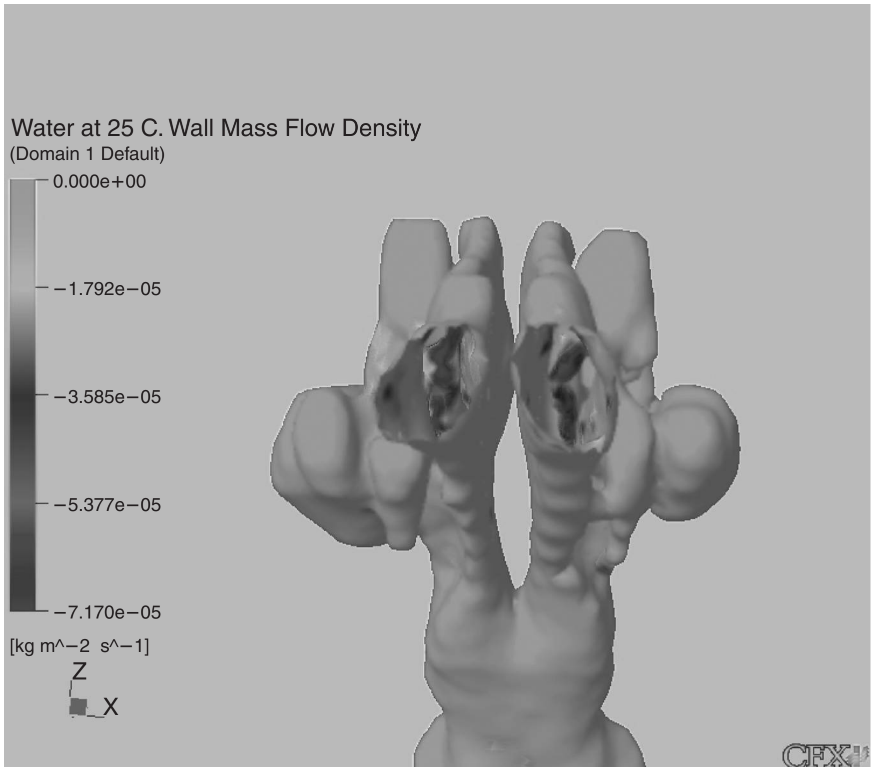

FIG. 12. Main aerosol depostion sites.

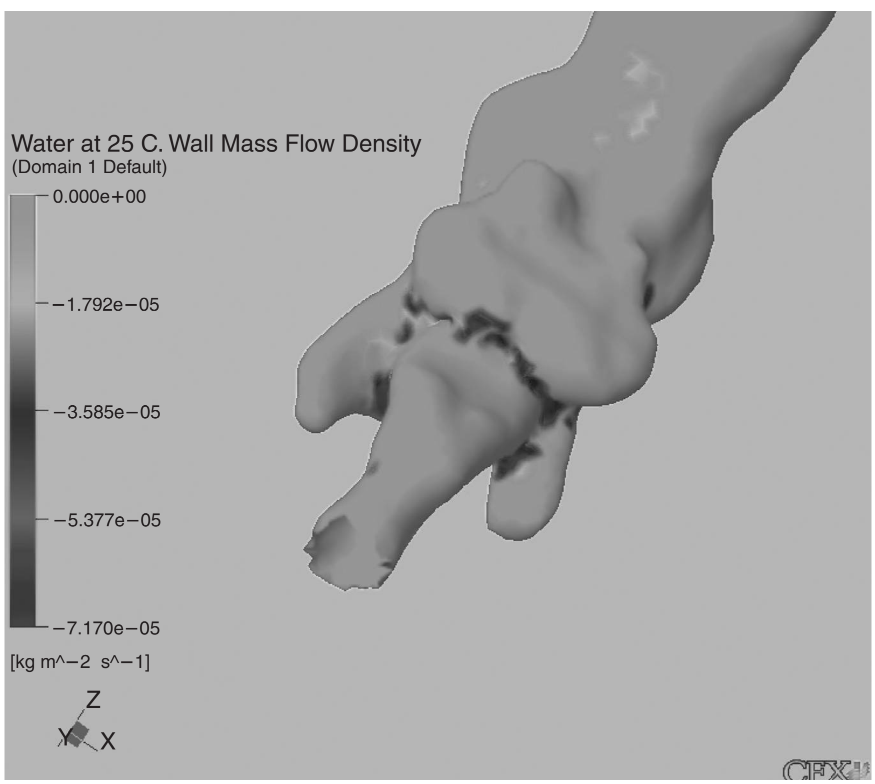

FIG. 13. Main aerosol deposition sites.

tions. For these experiments, the upper airways deposition (*SAINTdepos*) is calculated by:

$$SAINTdepos = \text{"Spacer output"} - \text{"Lung dose"} - \text{"Dose-on-facemask"}$$

The percentage of particles that is exhaled is not specified in these results. By calculating the upper airways deposition as in the equation above, the exhaled particles are included in the upper airways deposition percentage.

In Figure 11, the experimental and simulation results were plotted. For the simulation results, the accumulated (total) result is used for the comparison since they are included in the experimental results as well. Simulation results are low compared to experimental results. The decrease in deposition for higher TV's of the simulations compared to the increase in deposition of the experiments can be fully attributed to the decrease of the remaining particles in the simulations. Calculated upper airway deposition with 3.7-micron particles resulted in experimentally comparable values for low flow rates, but gave 50% lower results for higher flow rates.

The difference could be explained by several possible causes. The mean diameter of the particles used for the experiments could have been larger than 3.7 μm. However, a rerun with an MMAD of 5 μm for CFX did not give better results. Also discretization effects influence the flow in the simulations, as shown in the verification cases of the straight pipe. Also the geometry of the model used for the simulations is not the exact geometry used for the experiments. Especially the horizontal entrance at the nose and the absence of the facemask in the computational model will alter the direction of the entrance flow and thereby the likelihood of particle deposition just after this entrance.

Other deposition effects (e.g., electrostatic forces) are not included in the model and could be present during the experiments. Last but not least, the flow is influenced by turbulence effects. Especially for high velocities, turbulence will affect the deposition of aerosols. Inertial effects will cause more particles to leave the main flow and deposit onto the wall. New studies have to be performed to clarify the difference found between the results of the experiments and those of the computational program.

CONCLUSION

Comparing analytically calculated deposition fractions for sedimentation in a straight pipe and inertial impaction in a bend pipe with those of a commercial computational fluid dynamics package showed that, for 3- and 5-micron particles, similar results were found. However, for 1-micron particles, the error in the velocity field generated by an unstructured mesh became of the same order as the terminal settling velocity of these particles, thereby yielding inaccurate results.

At low flow rates, computational results of aerosol deposition in the upper airways of a young child with a commercial computational fluid dynamics package matched experimentally measured results. However, large deviations were found for higher flow rates and small particle sizes. Most probably, the incompletely modeled entrance at the nose of the particles and inertial effects due to turbulence might be responsible.

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