Inhalation Exposure Modeling for Assessing Health Risks of Toxic Aerosols and Vapors

Richard A. (Rick) Corley, Ph.D.
Greek Creek Toxicokinetics Consulting, LLC
Emeritus Laboratory Fellow, Pacific Northwest National Laboratory
Boise, Idaho
rcorley.gctc@gmail.com

CORESTA SSPT2021
NAM Symposium
19 October 2021

Modeling Examples for Inhaled Aerosols & Vapors

State-of-the-art inhalation modeling approaches for cross-species and *in vitro* to *in vivo* comparisons to assess human health risks

- 3D Imaging-based computational fluid dynamics (CFD) models of the respiratory system
- Incorporate species-specific 3D anatomy, physiology and clearance processes and realistic breathing and exposure scenarios for site-specific dosimetry

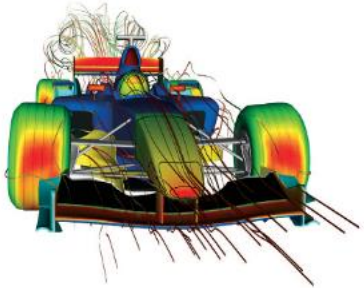
- **Ex 1: Ranking relative hazards of tobacco smoke constituents under a harm reduction strategy using existing animal toxicity and measured human exposure data**
  - CFD/PBPK modeling for cell- or tissue-specific internal dose
  - Corley et al., *Toxicol. Sci.* 146(2015)65-88

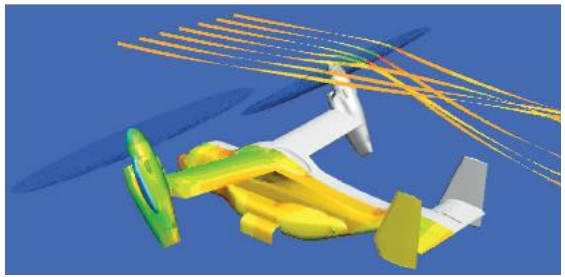
- **Ex 2: Reducing/replacing animal toxicity studies for pesticide re-registration with *in vitro* toxicity studies with human cells for occupational and residential exposures**
  - CFD/Aerosol/Mucociliary clearance modeling for region-specific retained dose
  - Corley et al., *Toxicol. Sci.* 182(2021)243-259

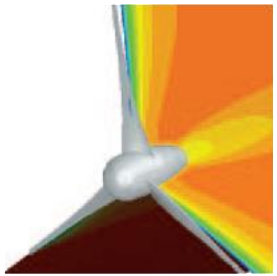
What is Computational Fluid Dynamics or CFD?

In a nutshell…

- **Numerical method for describing fluid flows**
  - Navier-Stokes Equations that describe the flow of a viscous fluid
  - Solved using a 3D computational mesh with appropriate boundary conditions (e.g. shape, mechanical properties, fluid characteristics, pressure, etc.)
  - The solution is a flow velocity field over space and time
  - Complexities added as needed (equations/mesh refinements) depending upon applications (e.g. physics of heat transfer, turbulence, material transport within fluids, material interactions, etc.)
- **Methods widely used in aerospace, automotive, energy, building HVAC, etc. industries to improve design, trouble-shooting, and decrease costs in product development**





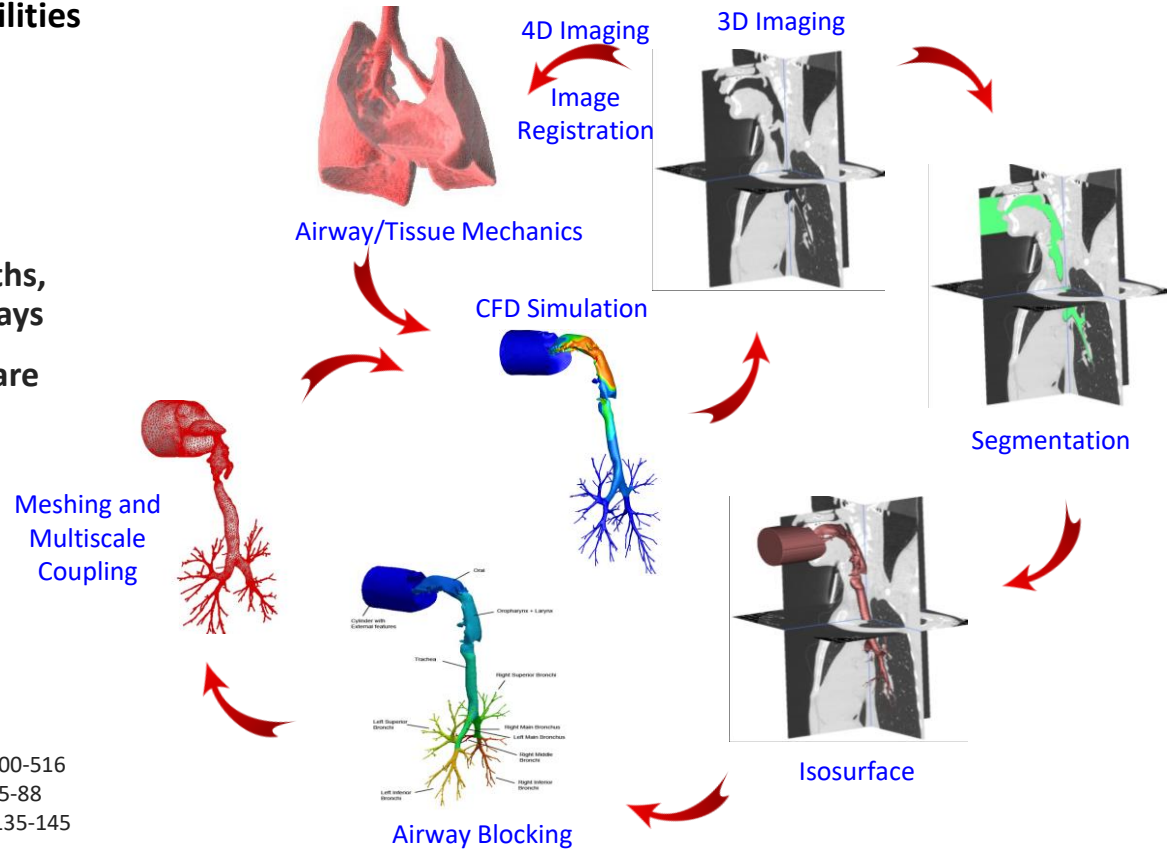


Source: Fluent News, 2005

What is Computational Fluid Dynamics or CFD?

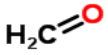
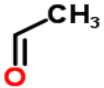
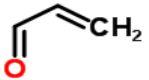
- **Biological applications are a rapidly growing area with the advent of new imaging, image analysis, and computational capabilities**

- **3D/4D MRI and CT**
  - Mod-High resolution
  - Dynamic
  - Structure & Function
- **What once took months, can now be done in days**
- **Personalized models are possible**



Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88
Jacob et al. Exp. Lung Res. 41(2014)135-145

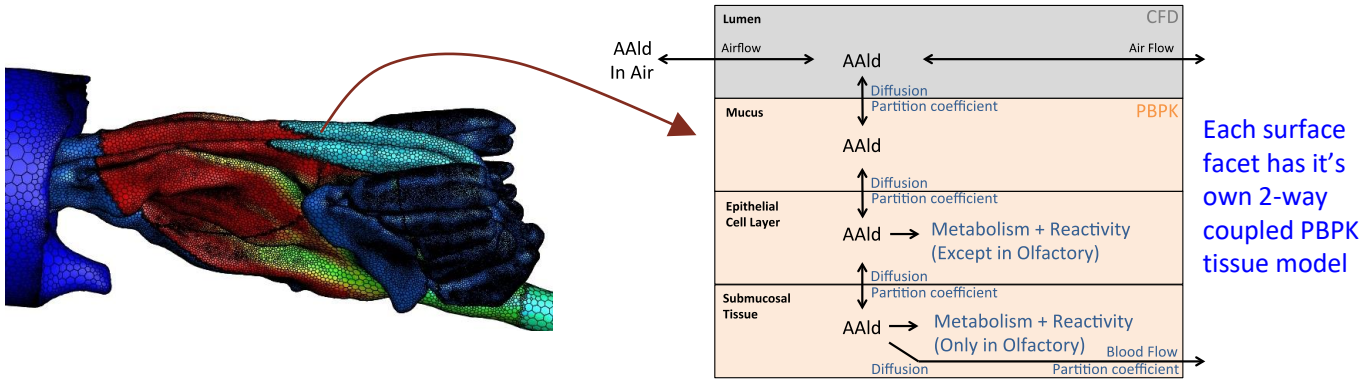
Ex 1: Multi-Scale CFD/PBPK for Reactive Aldehydes

Formaldehyde  Acetaldehyde  Acrolein 

- **Highly reactive, water-soluble vapors**
- **Important industrial chemical intermediates as well as by-products of combustion including smoking of tobacco products**
  - Difficult to directly measure in tissues, endogenously produced and have dietary sources of exposure
- **Cytotoxicity and tumors in specific sites within nasal and upper respiratory tissues of rodents drive many human health risk assessments**
- **Site-specificity of lesions and species differences in anatomy, physiology and tissue clearance rates warranted a combined CFD/PBPK approach**
  - Previous constituent risk comparisons often lacked species-, site-, or exposure-specific dosimetry considerations
- **Took advantage of existing CFD and PBPK models and realistic exposures to create a combined approach**

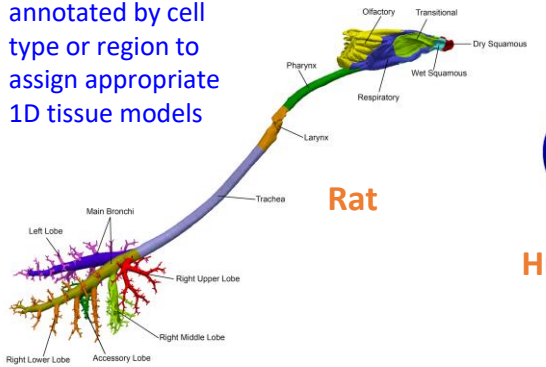
Ex 1: CFD/PBPK for Reactive Aldehydes

Model Structure

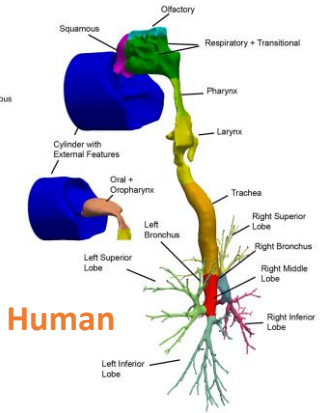


Each surface facet has it's own 2-way coupled PBPK tissue model

Airway surface is annotated by cell type or region to assign appropriate 1D tissue models



Rat



Human

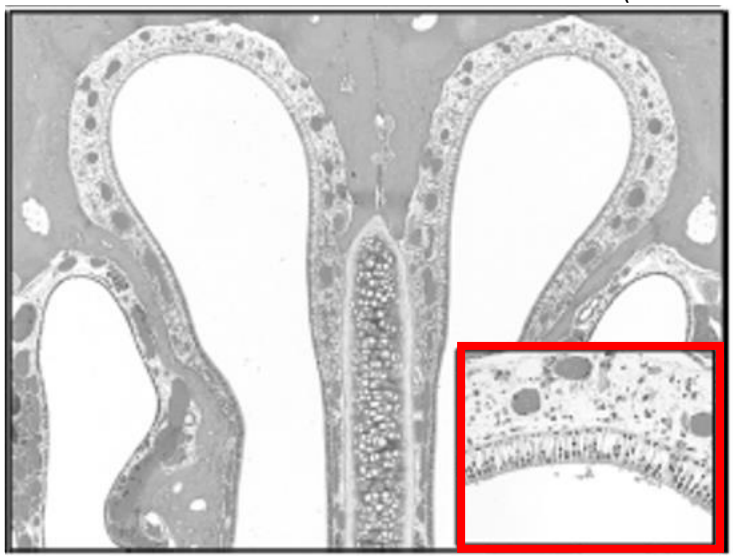
Corley et al. Toxicol. Sci. 128(2012)500-516
Corley et al. Toxicol. Sci. 146(2015)65-88

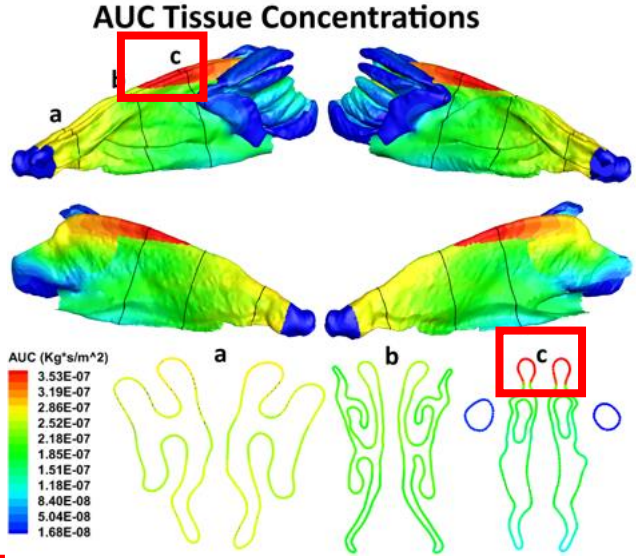
Ex 1: CFD/PBPK for Reactive Aldehydes

AUC Tissue Concentration “Hot Spots” vs. Lesions

Acetaldehyde

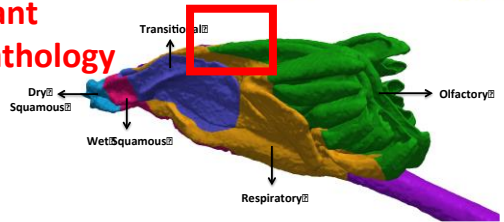
(Rat NOAEL = 50 ppm)





Enzyme Location is Key Determinant

➡AUC dosimetry maps to histopathology

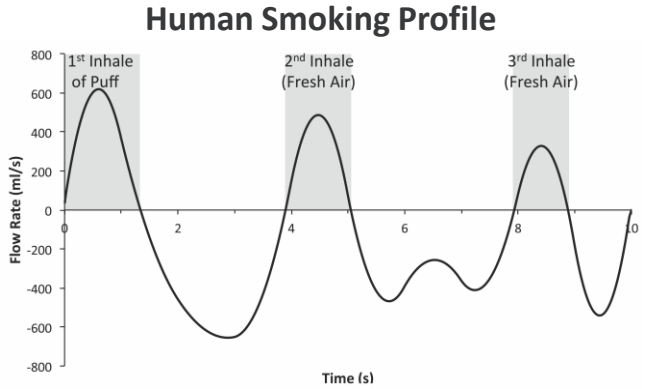


Corley et al. Toxicol. Sci. 146(2015)65-88

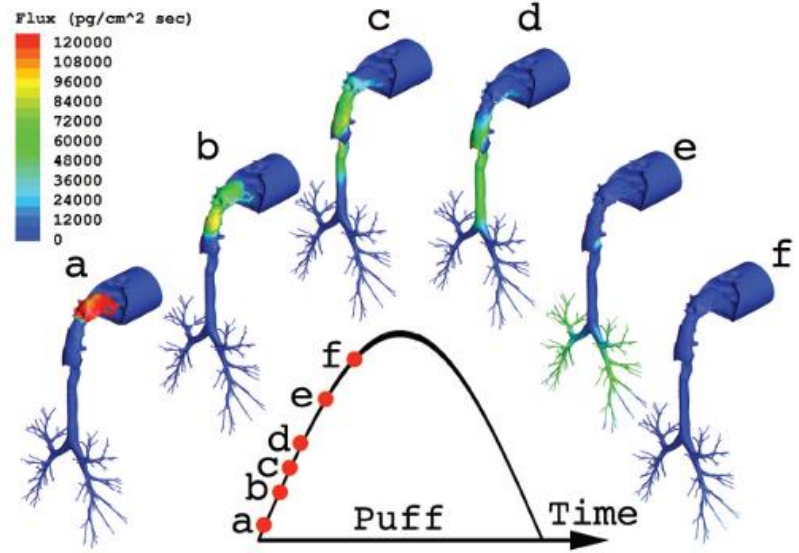
Dorman et al. Inhal. Toxicol. 20(2008)245-256

Ex 1: CFD/PBPK for Reactive Aldehydes

Human Exposure via Cigarette Smoking



- Measured human puff profile
  - St. Charles et al. Inhal. Toxicol. 21(2009)712-718)
- Measured smoke compositions for representative puff concentrations
  - (Counts et al. Reg. Toxicol. Pharmacol. 41(2005)185-227)
  - Acetaldehyde – 1028 ppm (857 µg/cig)
  - Acrolein – 94 ppm (100 µg/cig)
  - Formaldehyde – 108 ppm (61 µg/cig)



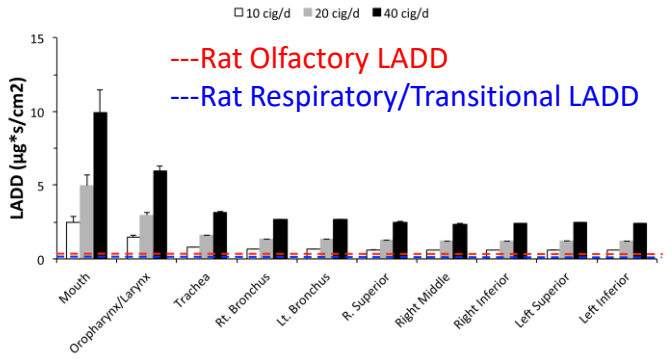
Corley et al. Toxicol. Sci. 146(2015)65-88

Ex 1: CFD/PBPK for Reactive Aldehydes

Comparative Dose Cigarette Smoke Constituents

Acrolein

(Rat NOAEL = 0.2 ppm; Puff = 94 ppm)



Rat - Human comparisons based upon 'Hot Spot' AUCs and Exposure-Duration/#cigs per day Adjustments

LADD Rat: NOAEL $AUC_{2.5\%}$/breath * bpm * 360 min/d * 5 d/7 d

LADD Human: $AUC_{2.5\%}$/puff * 11 puff/cig * no. cigs/d

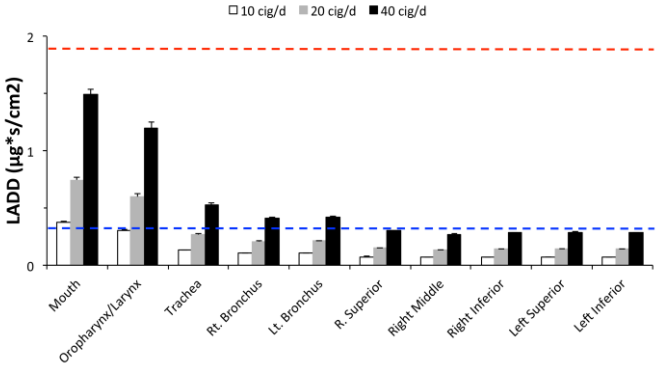
Rank order:

Acrolein > Formaldehyde > Acetaldehyde

No significant differences when simulated as a mixture with competitive metabolism

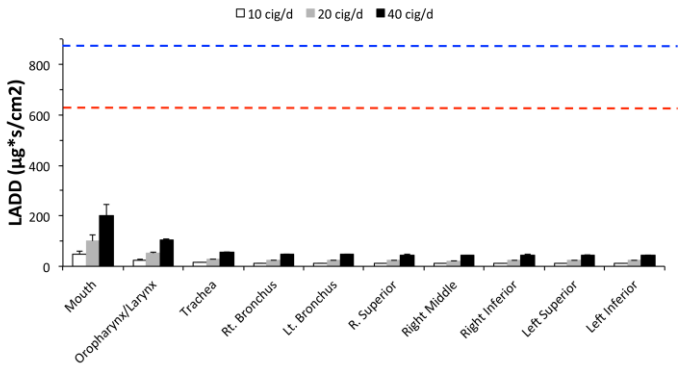
Formaldehyde

(Rat NOAEL = 1 ppm; Puff = 108 ppm)



Acetaldehyde

(Rat NOAEL = 50 ppm; Puff = 1024 ppm)



Ex 2: Syngenta's Pesticide Re-Registration
Chlorothalonil

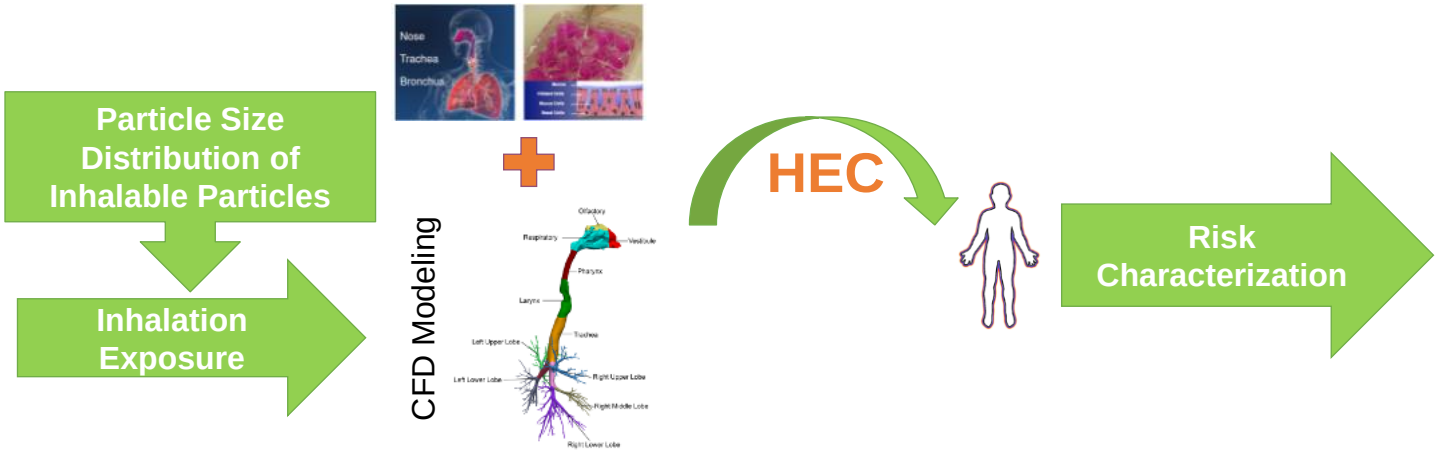
- **A widely-used fungicide since 1966**
  - Labeled for >65 crops
  - Also used as a wood protectant, anti-mold and anti-mildew agent, bacteriocide, microbiocide, algaecide and insecticide
- **Contact irritant by all routes of exposure**
- **Extremely low volatility and water solubility**
  - Formulated as a solid or liquid suspension
  - Applications typically water-diluted spray
- **Aerosol inhalation studies in rats with formulation (acute through 2-week)**
  - Epithelial degeneration/necrosis primarily in nose and larynx; minimal effects in trachea and lung
  - Squamous cell metaplasia in nose and larynx
  - Lesions resolved or reduced following 2-wk recovery

Ex 2: Syngenta's Pesticide Re-Registration

Inhalation Risk Assessment

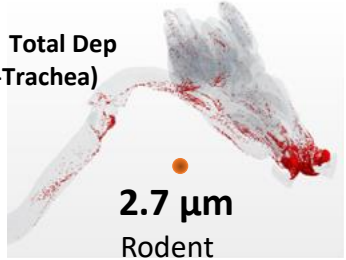
- **Replace requirement for 90-day rat inhalation toxicity study with *in vitro* studies in human cells coupled to enhanced characterization of exposure and target dose relevant to risk characterization**

***In vitro* Testing Based Point of Departure using MucilAir™ from Epithelix**



Ex 2: CFD/Particle Dosimetry for Cross-Species and IVIVE

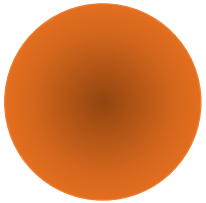
Oral Breathing

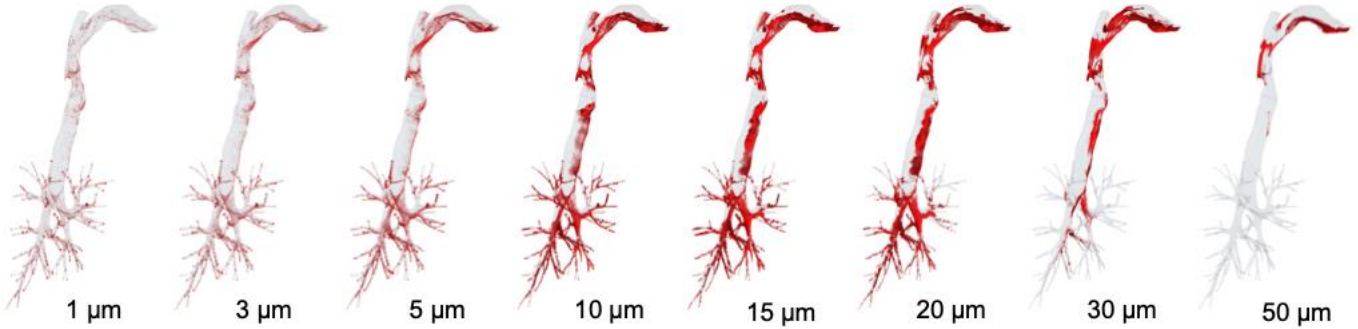


2.7 µm
Rodent
Study

13 µm
Mixer/Loader
Exposure

35 µm
Applicator
Exposure



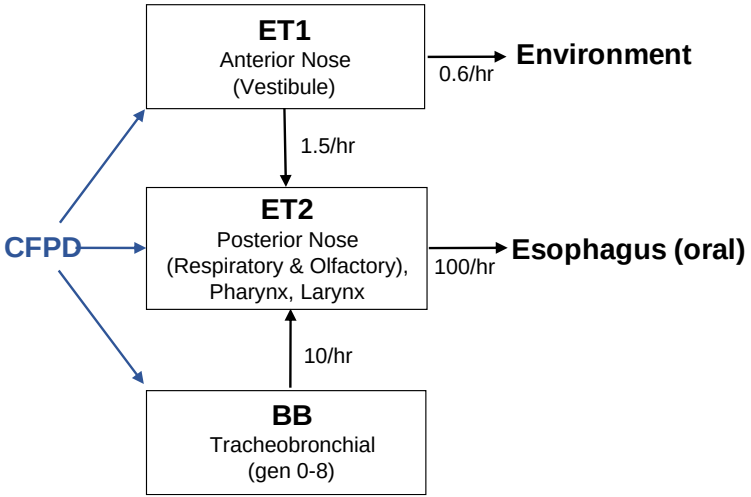


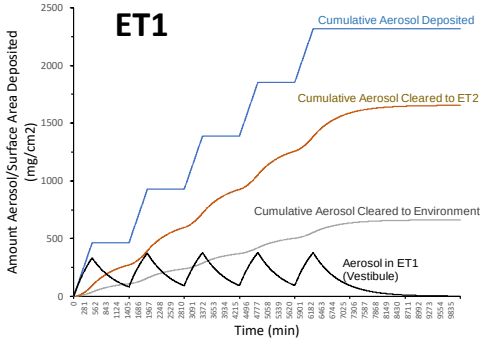
% Total Deposited (Mouth – Bronchi)

1.3	2.0	4.7	31.0	69.1	87.8	96.8	99.5

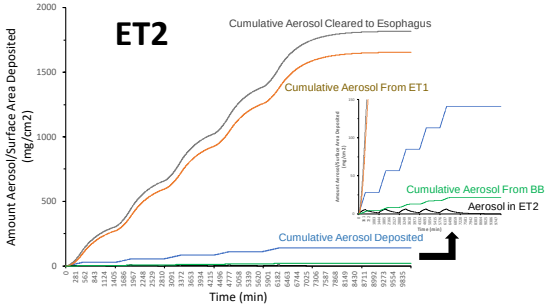
Ex 2: Clearance Model

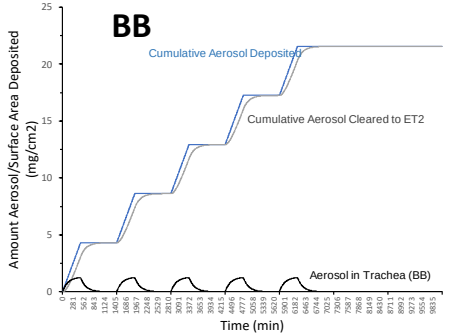
Abbreviated ICRP (2015)





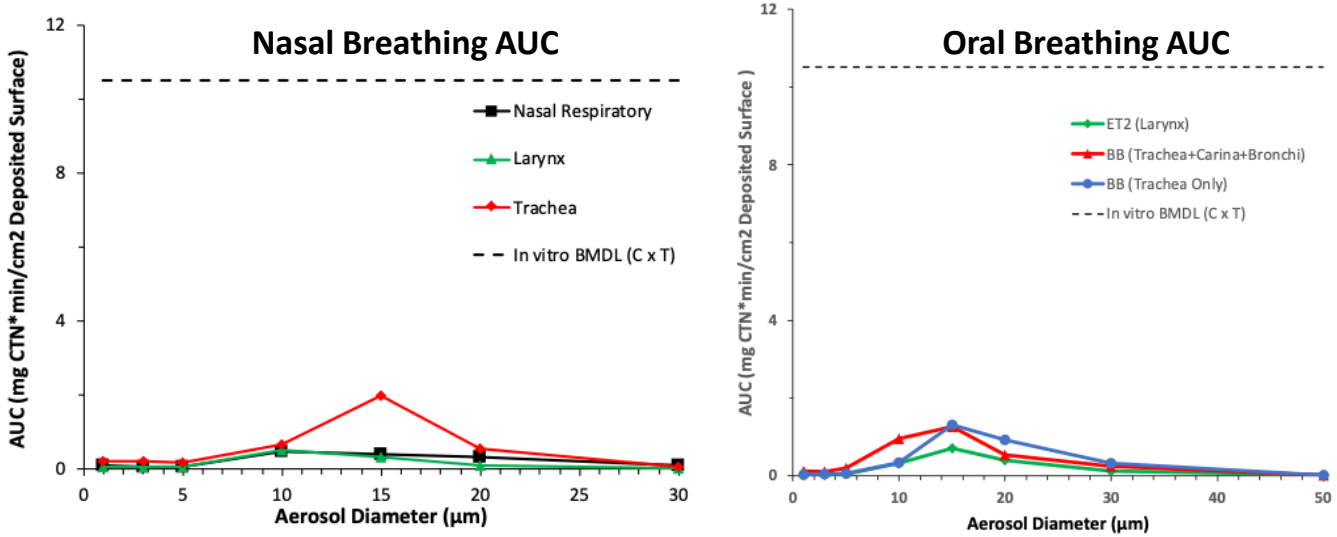
Ex: 10 µm Aerosols
8 hr/d, 5 d/wk





Ex 2: CFPD/CL Human Simulations at Rat LOAEL

AUC Retained Dose vs. In vitro BMDL



Exposures for 8-hr/day, 5 consecutive days followed by 2 days no exposure

- Day-to-day steady-state retention profile achieved in 2-3 days
- AUC retained doses determined for final exposure day
- AUC compared to BMDL*24 hr (CxT)
- HEC = (BMDL/AUC) * Aerosol Conc * Active Ingredient Conc

Corley et al. Toxicol Sci. 18(2021)243-259

Ex 2: Revised Human Risk Assessment for Inhalation Exposures

- **EPA determined the NAM using human *in vitro* data and CFPD dosimetry was appropriate for evaluating potential risk for inhalation exposure to direct contact irritants**
  - Waved requirement for additional 90-d rat inhalation studies (EPA, 2021).
  - Human equivalent concentrations (HEC) and human equivalent doses (HED) calculated for 2, 8 and 24-hr exposures based upon human *in vitro* BMDL's for multiple polydisperse aerosol scenarios
  - Interspecies UF reduced to 1X (both dosimetry and toxicity determined in human)
  - Intraspecies UF reduced to 3X (ADME not likely an impact for direct contact irritant/cytotoxicant)
  - Revised draft assessment and supporting documents open for comment until Sept. 20, 2021, at: https://www.regulations.gov/docket/EPA-HQ-OPP-2011-0840
    - Manuscripts for the human *in vitro* toxicity study (accepted) and human health risk assessment (in review) have also been submitted

Bottom Lines

- **CFD-based models are well-suited for calculating HEC's from *in vitro* and *in vivo* target tissue doses when site-specificity is important for inhalation toxicity (typically upper conducting airways)**
  - A valuable part of an overall toolkit for modeling inhalation exposures
- **These approaches have been used to refine human risk assessments as well as reduce or even replace animal studies by regulatory agencies**
- **Topics not covered but still important include:**
  - Model evaluation and verification/validation were key components to both examples
    - See references included at the end of this presentation including those used in the case studies
  - Models can be templated or adjusted to fit new materials or exposure scenarios (no need to start from scratch)
    - Airway geometries available for multiple humans and animal models (see Selected References)
    - Existing CFPD simulations are being used to predict site-specific doses for other aerosols that have similar properties
  - CFD models are ideal for site-specificity in upper conducing airways (nose/mouth to generation 5-10) but do not describe the deep lung due to limitations in imaging and the computational challenges
    - However, the Multiple Path Particle Dosimetry (MPPD) model is ideal for predicting regional dosimetry in the deep lung and is now being adopted by the U.S.EPA to replace its RDDR model
      - MPPD is available (free) at: https://www.ara.com/mppd/
    - CFPD models have also been linked with the MPPD model to provide full respiratory system coverage (Kuprat et al., *J. Aerosol Sci.* 151(2021)105647) and take advantage of, and compensate for, the strengths and weaknesses of each model
      - Ongoing work: disease influences on tissue mechanics are now being incorporated into the CFPD/MPPD model and validated against experimental data in humans and rats

Questions?

rcorley.gctc@gmail.com

Acknowledgments

- **Pacific Northwest National Laboratory (PNNL)**
  - Andrew Kuprat, Sarah Suffield, Senthil Kabilan (*Takeda), Kevin Minard (*Spintronics), Rick Jacob, Sean Colby, Dan Einstein (*St. Martin Univ.), James Carson (*Univ. Texas)
- **University of Washington**
  - Robb Glenny
- **UCSD**
  - Chantal Darquenne
- **Syngenta**
  - Tharacad S. (Rama) Ramanarayanan, Paul Hinderliter (*Axcella), Doug Wolf
- **Battelle Memorial Institute**
  - Kevin Yugulis
- **ARA**
  - Bahman Asgharian, Owen Price, Jeff Schroeter

- **Presented work funded by**
  - NHLBI, NIEHS, Battelle, RJR, DOE, Syngenta

Glossary

- **AUC = Area under the curve, typically of a concentration vs. time curve**
- **CFD = Computational fluid dynamics**
- **CFPD = Computational fluid-particle dynamics**
- **Cmax = Maximum concentration, typically of a concentration vs. time curve**
- **CT = X-ray computed tomography**
- **EPA = U.S. Environmental Protection Agency**
- **FIFRA SAP = Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel to EPA**
- **HEC = Human equivalent concentration (typically mg/L or mg/m^3)**
- **HED = Human equivalent dose (typically mg/kg/d)**
- **HVAC = Heating, ventilation, air conditioning**
- **ICRP = International Commission on Radiological Protection**
- **MMAD = Mass median aerodynamic diameter**
- **MPPD = Multiple path particle dosimetry model**
- **MRI = Magnetic resonance imaging**
- **NCRP = National Council on Radiation Protection**
- **PBPK = Physiologically based pharmacokinetic model**

Selected References

- Applied Computational Fluid Dynamics. (2005). Fluent News. Marshall, L., Ed. Vol. 14, Issue 2.
- Ardini-Poleske, M.E., Clark, R.F., Ansong, C., Carson, J.P., Corley, R.A., Deutsch, G.H., Hagood, J.S., Kaminski, N., Mariani, T.J., Potter, S.S., Pryhuber, G.S., Warburton, D., Whitsett, J.A., Palmer, S.M., Ambalavanan, N., LungMAP Consortium. (2017). LungMAP: The molecular atlas of lung development program. Amer. J. Phys. Lung Cell. Mol. Physiol. 313, 733-740.
- Behrsing, H., Hill, E., Raabe, H., Tice, R., Fitzpatrick, S., Devlin, R., Pinkerton, K., Oberdorster, G., Wright, C., Wieczorek, R., Aufderheide, M., Steiner, S., Krebs, T., Asgharian, B., Corley, R., Oldham, M., Adamson, J., Li, X., Rahman, I., Grego, S., Chu, P.H., McCullough, S., and Curren, R. (2017). In Vitro Exposure Systems and Dosimetry Assessment Tools for Inhaled Tobacco Products: Workshop Proceedings, Conclusions and Paths Forward for In Vitro Model Use. ATLA 45, 117-158.
- Colby, S.M., Kabilan, S., Jacob, R.E., Kuprat, A.P., Einstein, D.R., Minard, K.R., and Corley, R.A. (2016). Comparison of realistic and idealized breathing patterns in computational models of airflow and vapor dosimetry in the rodent upper respiratory tract. Inhal. Toxicol. 28(4), 192-202.
- Corley, R.A., Kabilan, S., Kuprat, A.P., Carson, J.P., Jacob, R.E., Minard, K.R., Teeguarden, J.G., Timchalk, C., Pipavath, S., Glenny, R., and Einstein, D.R. (2015). Comparative risks of aldehyde constituents in cigarette smoke using transient computational fluid dynamics/physiologically based pharmacokinetic models of the rat and human respiratory tracts. Toxicol. Sci., 146(1), 65-88.
- Corley, R.A., Kabilan, S., Kuprat, A.P., Carson, J.P., Minard, K.R., Jacob, R.E., Timchalk, C., Glenny, R., Pipavath, S., Cox, T., Wallis, C., Larson, R.F., Fanucchi, M.V., Postlethwait, E., and Einstein, D.R. (2012). Comparative computational modeling of airflows and vapor dosimetry in the respiratory tracts of rat, monkey, and human. Toxicol. Sci., 128(2), 500-516.
- Corley, R.A., Kuprat, A.P., Suffield, S., Kabilan, S., and Hinderliter, P., Yugulis, K. and Ramanarayanan, T.S. (2021). New approach methodology for assessing inhalation risks of a contanct respiratory cytotoxicant: computational fluid-particle dynamic-based aerosol dosimetry modeling for cross-species and in vitro comparisons. Toxicol. Sci. 182(2), 243-259.
- Counts, M. E., Morton, M. J., Laffoon, S. W., Cox, R. H., Lipowicz, P.J. (2005). Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regul. Toxicol. Pharmacol., 41,185–227.
- Dorman, D. C., Struve, M. F., Wong, B. A., Gross, E. A., Parkinson, C., Willson, G. A., Tan, Y. M., Campbell, J. L., Teeguarden, J. G., Clewell, H. J., 3rd, et al. (2008a). Derivation of an inhalation reference concentration based upon olfactory neuronal loss in male rats following subchronic acetaldehyde inhalation. Inhal. Toxicol., 20, 245–256.
- EPA (U.S. Environmental Protection Agency), 2016. Process for evaluating & implementing alternative approaches to traditional in vivo acute toxicity studies for FIFRA regulatory use. Office of Pesticide Programs, Washington, DC. February 4, 2016.
- EPA (U.S. Environmental Protection Agency), 2018. Strategic plan to promote the development and implementation of alternative test methods within the TSCA program. EPA-740-R1-8004. June 22, 2018.

Selected References (continued)

- ICRP (International Commission on Radiological Protection), 2015. Occupational intakes of radionuclides: Part 1. ICRP Publication 130. Ann. ICRP 44(2). Sage.
- Jacob, R.E., Lamm, W.J., Einstein, D.R., Krueger, M.A., Glenny, R.W. and Corley, R.A. (2014). Comparison of CT-derived ventilation maps with deposition patterns of inhaled microspheres in rats. Exp. Lung Res. 41, 135-145.
- Kabilan, S., Suffield, S.R., Recknagle, K.P., Jacob, R.E., Einstein, D.R., Kuprat, A.P., Carson, J.P., Colby, S.M., Saunders, J.H., Hines, S.A., Teeguarden, J.G., Straub, T.M., Moe, M., Taft, S.C. and Corley, R.A. (2016). Computational fluid dynamics modeling of Bacillus anthracis spore deposition in rabbit and human respiratory airways. J. Aerosol Sci., 99, 64-77.
- Kimbell, J.S., Godo, M.N., Gross, E.A., Joyner, D.R., Richardson, R.B., and Morgan, K.T. (1997). Computer simulation of inspiratory airflow in all regions of the F344 rat nasal passages. Toxicol. Appl. Pharmacol. 145, 388-398.
- Kimbell, J.S., Subramaniam, R.P., Gross, E.A., Schlosser, P.M. and Morgan, K.T. (2001). Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. Toxicol. Sci. 64, 100-110.
- Kolanjiyil, A. and Kleinstreuer, C., 2016. Computationally efficient analysis of particle transport and deposition in a human whole-lung airway model. Part 1: theory and model validation. Computers Biol. Med. 79, 193-204.
- Kolanjiyil, A. and Kleinstreuer, C., 2017. Computational analysis of aerosol-dynamics in a human whole-lung airway model. J. Aerosol Sci. 114, 301-316.
- Kuprat, A.P., Jalali, M., Jan, T., Corley, R.A., Asgharian, B., Price, O., Singh, R.K., Colby, S., and Darquenne, C. (2021). Efficient bi-directional coupling of 3D Computational Fluid-Particle Dynamics and 1D Multiple Path Particle Dosimetry lung models for multiscale modeling of aerosol dosimetry. J. Aerosol Sci. 151, 105647
- Longest, P.W., Bass, K., Dutta, R., Rani, V., Thomas, M.L., El-Achwah, A. and Hindle, M. (2019) Use of computational fluid dynamics deposition modeling in respiratory drug delivery, Expert Opinion on Drug Delivery, 16:1, 7-26.
- Longest, P. W., and Holbrook, L. T. (2011). In silico models of aerosol delivery to the respiratory tract - Development and applications. Adv. Drug Deliv. Rev. 64, 296–311.
- Longest, P.W., Tian, G., Walenga, R.L. & Hindle, M. (2012). Comparing MDI and DPI aerosol deposition using in vitro experiments and a new stochastic individual path (SIP) model of the conducting airways. Pharm. Res. 29, 1670–1688.
- Lucci, F., Castro, N., Rostami, A., Oldham, M., Hoeng, J., Pithawalla, Y., Kuczaj, A. (2018). Characterization and modeling of aerosol deposition in Vitrocell® exposure systems - exposure well chamber deposition efficiency. J. Aerosol Sci. 123, 141-160.
- Martonen, T. B., and Schroeter, J. D. (2003). Risk assessment dosimetry model for inhaled particulate matter: I. Human subjects. Toxicol. Lett. 138, 119–132.
- Martonen, T. B., and Schroeter, J. D. (2003). Risk assessment dosimetry model for inhaled particulate matter: II. Laboratory surrogates (rat). Toxicol. Lett. 138, 133–142.

Selected References (continued)

- Minard, K. R., Einstein, D. R., Jacob, R. E., Kabilan, S., Kuprat, A. P., Timchalk, C. A., Trease, L. L., and Corley, R. A. (2006). Application of magnetic resonance (MR) imaging for the development and validation of computational fluid dynamic (CFD) models of the rat respiratory system. Inhal. Toxicol. 18, 787–794.
- National Academy of Sciences (NAS). (2007). Toxicity testing in the 21st century: a vision and a strategy. National Academy Press. Washington, D.C.
- National Academy of Sciences (NAS). (2012). Exposure science in the 21st century: a vision and a strategy. National Academy Press. Washington, D.C.
- NIH/NHLBI LungMAP Consortium: Molecular and Cellular Atlas of Lung Development. www.lungmap.net.
- Schroeter, J.D., Kimbell, J.S., Gross, E.A., Willson, G.A., Dorman, D.C., Tan, Y.M., and Clewell, H.J. (2008). Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. Inhal. Toxicol. 20, 227-243.
- St Charles, F. K., Krautter, G. R., and Mariner, D. C. (2009). Postpuff respiration measures on smokers of different tar yield cigarettes. Inhal. Toxicol., 21, 712–718
- Walenga, R.L., Babiskin, A.H., and Zhao, L. 2019. In silico methods for development of generic drug-device combination orally inhaled drug products. CPT Pharmacometrics Syst. Pharmacol. 8, 359-370.
- Xi, J., Kim, J.W., Si, X.A., Corley, R.A., and Zhou, Y. (2016). Modeling of inertial depositions in scaled models of rat and human nasal airways: Towards in vitro regional dosimetry in small animals. J. Aerosol. Sci. 99, 78-93.
- Yin, Y., Choi, J., Hoffman, E.A., Tawhai, M.H., and Lin C.L., 2010. Simulation of pulmonary air flow with a subject-specific boundary condition. J. Biomech. 43, 2159-2163.
- Yin, Y., Choi, J., Hoffman, E.A., Tawhai, M.H., and Lin C.L., 2013. A multiscale MDCT image-based breathing lung model with time-varying regional ventilation. J. Comp. Phys. 244, 168-192.
- **NAM Links:**
  - EPA: https://www.epa.gov/research/epa-new-approach-methods-efforts-reduce-use-animals-chemical-testing
  - FDA: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-publishes-report-advancing-alternative-methods