Using CFD Modeling and Dosimetry as a Framework to Incorporate Endogenous Formation into a Chemical Assessment

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Endogenous Chemical Risk Assessment: Formaldehyde as a Case Example

Background

- Formaldehyde is an endogenous compound that is present in human blood and tissues

- Formaldehyde has been measured in exhaled breath at concentrations of several parts per billion
  - indicates off-gassing of formaldehyde from respiratory tissues

- National Research Council (2009): *“The endogenous production of formaldehyde complicates the assessment of the risk associated with formaldehyde inhalation and remains an important uncertainty in assessing the additional dose received by inhalation”*

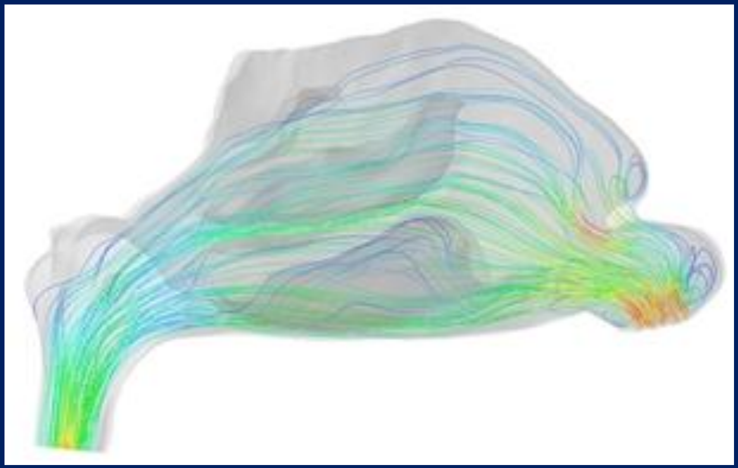
Purpose

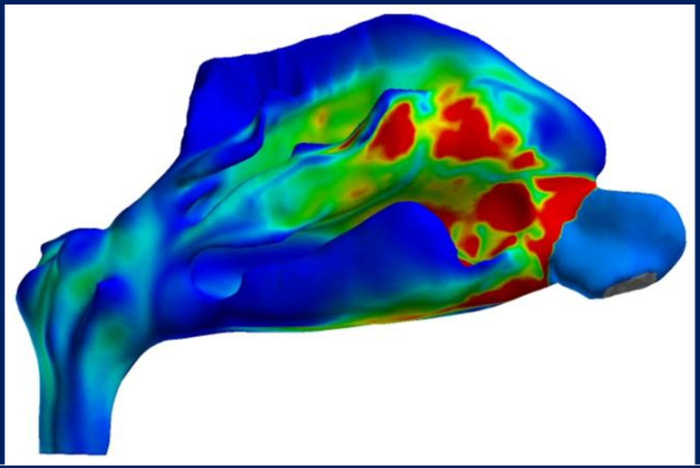
Quantify the target tissue dosimetry of inhaled exogenous formaldehyde in the nasal passages in the presence of endogenous formaldehyde

- Computational fluid dynamics (CFD) models of the nasal passages of a rat, monkey, and human were used to simulate inhaled formaldehyde in the presence of endogenous formaldehyde in nasal tissues

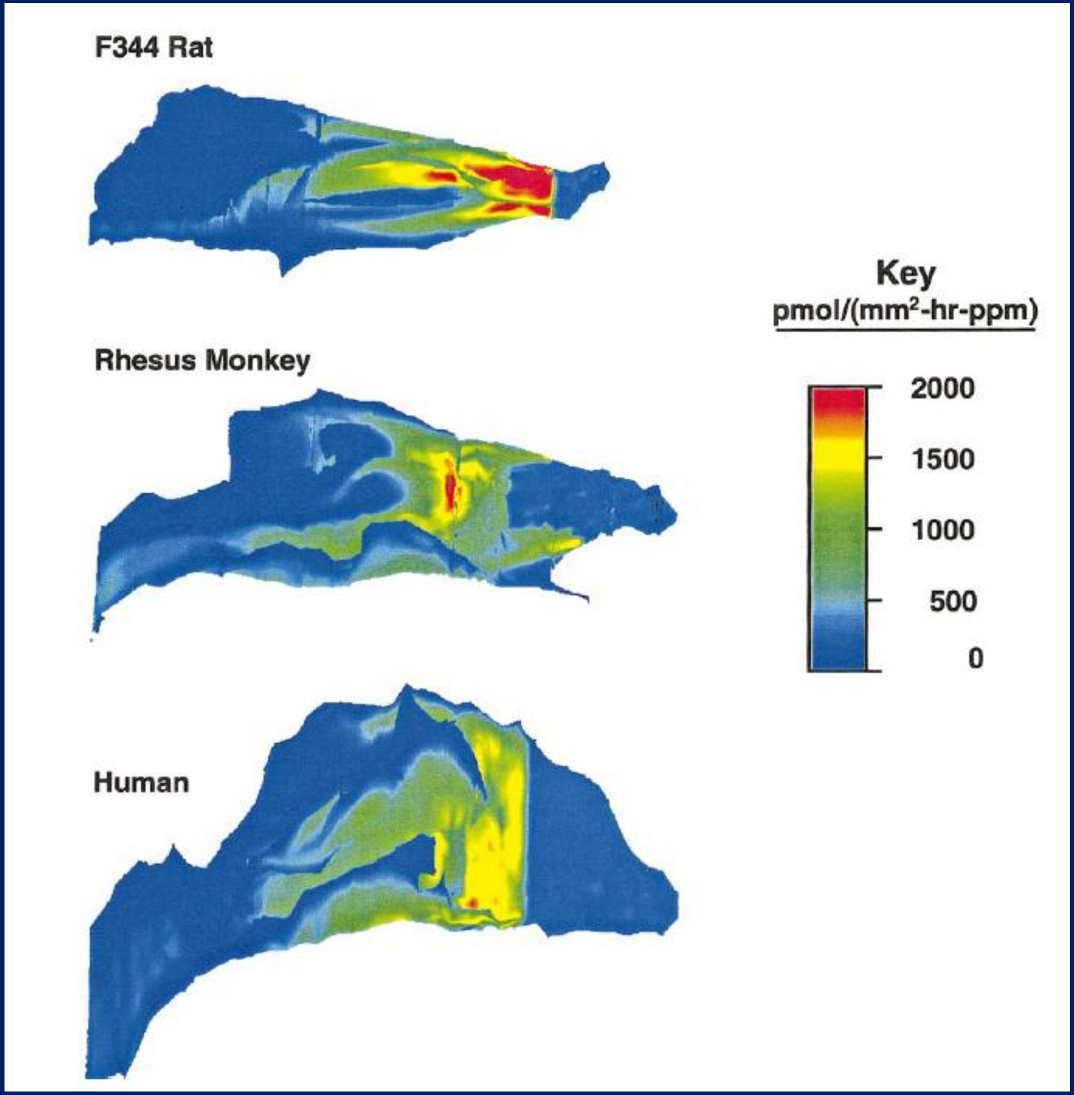
CFD Modeling of Vapor Uptake

- Develop 3D reconstructions of the model surface -- rat, monkey, and human nasal passages
- Solve airflow equations in each species
- Apply boundary conditions and simulate vapor uptake
- Analyze wall mass flux patterns and site-specific flux





Formaldehyde Nasal Dosimetry Modeling



From Kimbell et al. (2001)

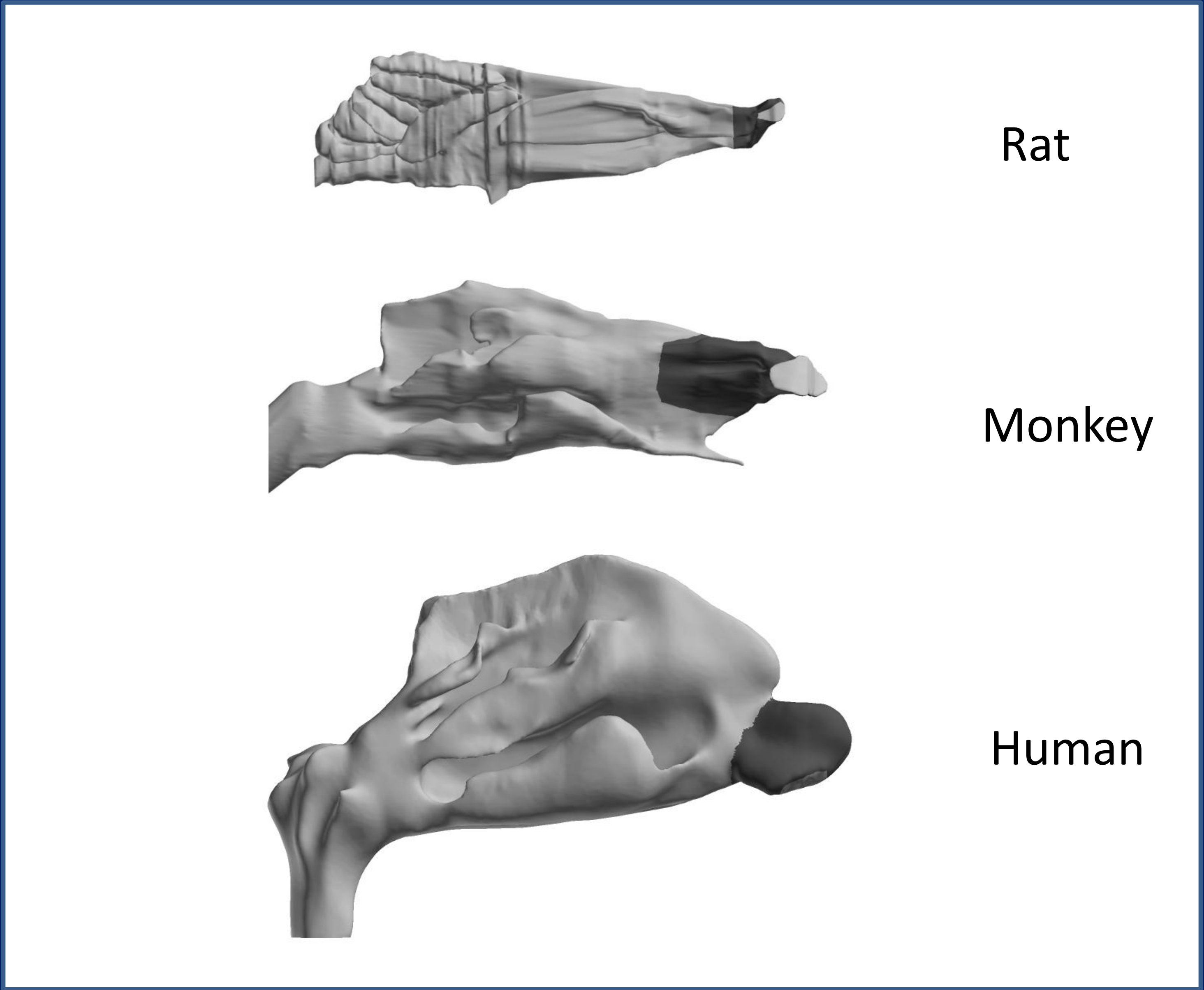
Strengths

- Anatomically accurate reconstructions of the nasal airways were used to simulate the complex airflow patterns and nonlinear formaldehyde uptake
- Site-specific flux predictions were obtained for comparisons across species

Limitations

- Mass transfer rates were calibrated to formaldehyde rat nasal uptake measurements at high exposure concentrations (> 2 ppm)
- Endogenous formaldehyde cannot be incorporated into the models using this approach

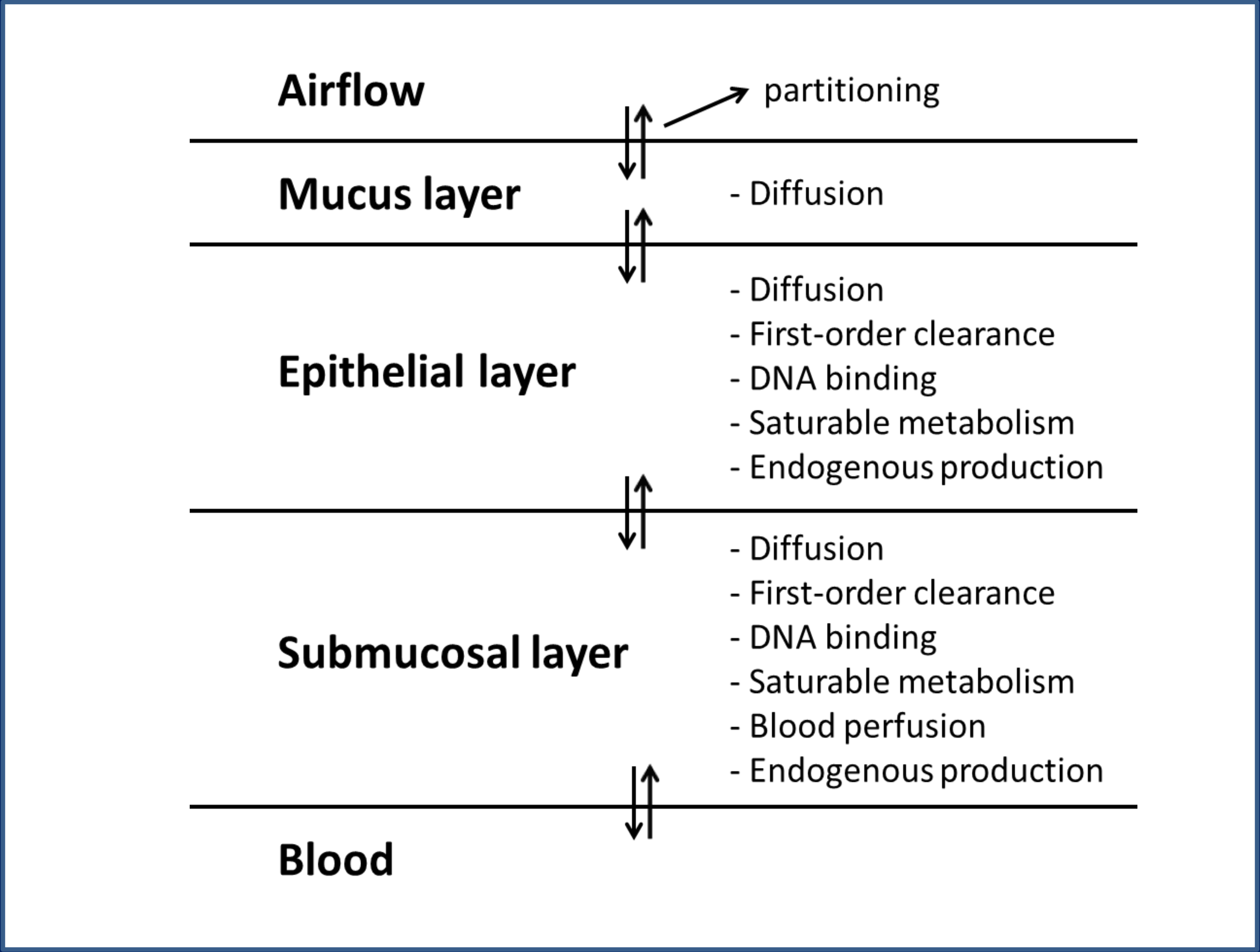
Interspecies Nasal CFD Models



Updates to Kimbell et al. (2001) Models

- Smoother surface contours in the rat and monkey models
- New human nasal model based on high-res CT scans
- High-density numerical meshes for improved accuracy
- Modified boundary condition to include formaldehyde pharmacokinetics and endogenous production

Formaldehyde Mass Transfer



Implement a mass transfer boundary condition based on formaldehyde kinetics:

- Physico-chemical properties: diffusivity, partitioning
- Clearance properties: parameters from Conolly et al. (2000)
- Endogenous production: rate constant in each species calibrated to nasal tissue levels

The modified nasal CFD models are capable of predicting site-specific formaldehyde absorption or desorption (off-gassing) depending on formaldehyde air and mucosal concentrations

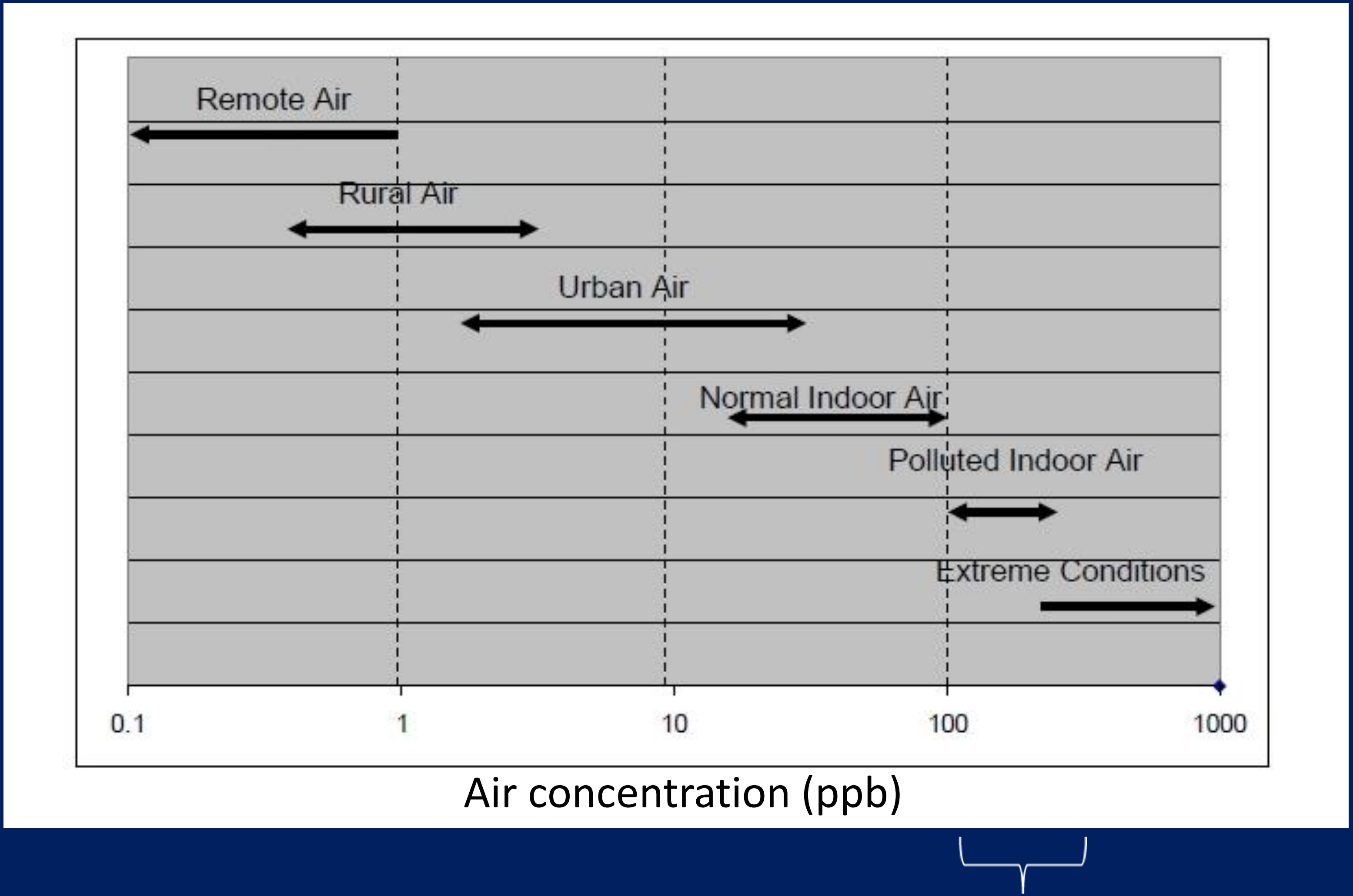
Formaldehyde Dosimetry Simulations

- Steady-state inspiratory airflow was simulated in each model at flow rates equal to twice estimated minute volume for resting breathing
- Formaldehyde uptake was simulated using the mass transfer approach based on formaldehyde kinetics (including endogenous production)
- Endogenous formaldehyde production rates were calibrated to yield nasal mucosal concentrations of 0.4 μmol/g
- Formaldehyde uptake simulations were conducted at exposure concentrations from 0.001 – 10 ppm

Formaldehyde Nasal Uptake

Exposure Concentration (ppm)	Nasal Uptake (%)		
	Rat	Monkey	Human
1.0	99.4	86.5	85.3
0.1	98.6	86.5	84.7
0.01	91.3	84.1	77.1
0.001	17.5	42.8	n/a[1]

Formaldehyde Exposure Levels



From Salthammer et al. (2010)

CFD Outputs to BBDR Model

- Rat, monkey: Average flux values were computed in regions where DPX and cell proliferation were measured
  - exposure concentrations: 0.7, 2, 6, 10, 15 ppm

- Human: A flux binning procedure was applied to partition the human nasal surface into regions of similar flux
  - exposure concentrations: 0.001 – 1 ppm

Conclusions

- Nasal uptake of inhaled formaldehyde is high (> 85%) at exposure concentrations > 500 ppb
- The presence of endogenous formaldehyde did not affect formaldehyde absorption at exposure concentrations > 500 ppb
- Reduced nasal tissue dose was predicted at exposure concentrations < 500 ppb due to the presence of endogenous formaldehyde
- Sharply reduced tissue dose was predicted at exposure concentrations < 10 ppb
- Net desorption of formaldehyde was predicted in humans at exposure concentrations ≤ 1 ppb

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