USER STORY

Researchers Use Simulink® Models to Predict Cancer Risk from Formaldehyde Exposure

How high is your risk of getting cancer if you inhale formaldehyde? Dr. Rory Conolly, a research toxicologist at the CIIT Centers for Health Research in North Carolina, constructs biologically-based simulation models in an attempt to answer that question.

Formaldehyde is used in many building materials and household products. Laboratory experiments on rats show that formaldehyde leads to nasal cancer if inhaled in high concentrations for long periods. This data has raised concern that workers and others exposed to formaldehyde may also be vulnerable.

Dr. Conolly uses MathWorks tools to analyze data from toxicology experiments on laboratory animals and to develop a simulation model to predict the potential human risk.

THE CHALLENGE

Most inhaled formaldehyde is absorbed in the lining of the nose, where it penetrates the nuclei of the cells and forms DNA-protein cross-links (DPX). DPX are thought to play a role in the development of formaldehyde-induced tumors. Conolly and his team knew that accurately predicting DPX levels in humans exposed to formaldehyde would improve their ability to predict human cancer risk. However, since humans cannot be used as test subjects, they would need to extrapolate findings in laboratory animals to humans in order to meet this objective.

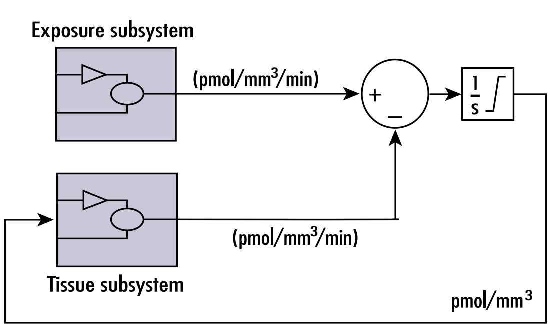
Previous work on this problem included development of anatomically rich, computational fluid dynamic (CFD) models built from rat, monkey, and human data. These models describe how the complex anatomy of the nasal passages affects airflow patterns in the nose. The airflow patterns determine how much formaldehyde is delivered by inhaled air to the tissue lining the airways.

Conolly needed research tools that would provide a tightly integrated environment and enable configurable simulation runs, statistical optimization, and the post-processing of results.

THE SOLUTION

For this project, Conolly chose MATLAB® and Simulink® because they provide a powerful environment for the development of physiologically based pharmacokinetic models. MATLAB's graphics are also important to the simulation process, as visualization is often the most convenient means of understanding model behavior. Conolly also used the Optimization Toolbox to determine unknown parameter values in the model by fitting the model to DPX data.

First, Conolly's team developed a Simulink model of DPX formation in the tissue, using CFD model predictions of formaldehyde delivery as inputs. Using Simulink's hierarchical design structure, the team built the DPX simulation model as a simple, two-subsystem structure.



Schematic of the Simulink DPX model: The exposure subsystem measures the timing and duration of formaldehyde exposure. The tissue subsystem measures formaldehyde clearance and DPX formation.

THE CHALLENGE

To analyze existing research data in order to assess the cancer risk for humans exposed to formaldehyde

THE SOLUTION

Use MathWorks tools to model and simulate the body's reaction to formaldehyde and generate reproducible results

THE RESULTS

- New insight into the effects of formaldehyde exposure
- Reliable diagnostic research tool
- Improved workplace safety standards

> *MATLAB's Optimization Toolbox and Simulink help us evaluate the latest science on inhaled formaldehyde and bridge the gap between laboratory research and risk assessment.*
>
> Dr. Rory Conolly,
> CIIT Centers for Health Research

The exposure subsystem described the timing and duration of exposure to formaldehyde and the rate at which formaldehyde moved into the nasal tissue. The tissue subsystem described the fate of formaldehyde within the tissue by either binding to DNA to form DPX or escaping through other processes. These two subsystems were connected by summation and integrator blocks. The overall Simulink DPX model predicts DPX concentration in the tissue as a function of the concentration of formaldehyde in the inhaled air. The identical model structure was used for rats, rhesus monkeys, and humans, with some modifications to parameter values.

Conolly's team then linked the Simulink model to MATLAB and the Optimization Toolbox. The parameters for the rats and monkeys were either measured directly in the laboratory or identified by optimization against DPX data. The human model structure relied largely on extrapolation of parameter values from the rat and monkey models, since no human DPX data was available.

By optimizing the Simulink model against DPX data and adjusting parameters for human cases, Conolly could then predict DPX levels in humans. From the many optimization algorithms available in the Optimization Toolbox, Conolly chose `fmincon` for this work as the fitting was done with constraints and with a modified least squares cost function. Monte Carlo sampling was used to identify some parameter values. At each iteration of Monte Carlo sampling, the remaining adjustable parameters were identified by optimization. A thousand Monte Carlo iterations and associated optimizations were used to identify the set of optimal parameters. The optimization was controlled from scripts written as MATLAB M-files, and results were visualized using MATLAB graphics. The ability to smoothly combine the Simulink model with MATLAB code for optimization and Monte Carlo sampling was key to the project's success.

"The Simulink model enabled us to more accurately predict human nasal mucosal DPX resulting from formaldehyde inhalation," notes Conolly.

THE RESULTS

- **New insight into the effects of formaldehyde exposure.** "Pharmacokinetic models using tools like Simulink have important potential applications in the prediction of human health risk from exposure to man-made chemicals and in the development of new pharmaceuticals" Conolly says.
- **A reliable diagnostic research tool.** The Simulink model confirmed that predicted levels of nasal mucosal DPX for a given inhaled concentration of formaldehyde in rats and monkeys, when extrapolated to humans, would enable researchers to predict human risk.
- **Improved workplace safety standards.** Government agencies, including Health Canada and the US Environmental Protection Agency, will use Conolly's findings to help establish environmental standards for formaldehyde usage—ultimately ensuring a safer workplace. ■

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