TOXICOLOGICAL HIGHLIGHT

The Use of Nasal Dosimetry Models in the Risk Assessment of Inhaled Gases

Jeffry D. Schroeter¹

The Hamner Institutes for Health Sciences, Research Triangle Park, North Carolina

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Nasal dosimetry models, including physiologically based pharmacokinetic (PBPK) models, computational fluid dynamics (CFD) models, and hybrid CFD-PBPK models, have played a prominent role in inhalation toxicology and the risk assessment of inhaled gases. Although different in their approach, their goals are similar: to accurately describe tissue dosimetry of inhaled gases in an anatomically accurate representation of the complex nasal geometry. These models have been useful in elucidating dose-response behavior and enabling interspecies extrapolation of regional dose that may differ between laboratory animals and humans. This issue of Toxicological Sciences includes an insightful paper by Morris and Hubbs (2009) on the use of a hybrid CFD-PBPK model to describe inhalation dosimetry of two components of butter flavoring vapors: diacetyl and butyric acid. These investigators used in vitro studies of diacetyl metabolism, nasal uptake data of inhaled diacetyl in rats, and pathology data from an in vivo study to correlate simulation results for localized tissue concentration with regional pathology scores as a basis for a quantitative risk assessment of inhaled diacetyl.

Many toxic gases elicit effects in the nasal passages of rodents because the nose is the first line of defense against inhaled materials in obligate nose-breathing animals. Gases that are highly soluble or reactive in nasal tissues will be mostly absorbed in the nose with strong localized dosimetric gradients, whereas gases with low solubility or those that are not as reactive have lower and more uniform absorption rates, allowing higher concentrations to reach the lungs. Regardless of its physico-chemical characteristics, gases are transported through the nose by inhaled airstreams, which are determined by the complex shape of the nose, dividing the bulk airflow into several primary airflow streams (Kimbell et al., 1997a; Morgan and Monticello, 1990). These factors lead to distinct regional deposition patterns, which, if they can be predicted, can be useful in evaluating inhalation risk. It is these characteristics of geometry, airflow, and regional deposition that nasal dosimetry models simulate.

Hybrid CFD-PBPK models use information on airflow allocation and air-phase mass transfer rates derived from CFD models (Kimbell et al., 1997a) in a compartmental division of the nasal airspace and tissues. This compartmental structure of the nose based on locations of major airflow streams and epithelial types was developed by Morris et al. (1993) and has since been used in numerous other studies of inhaled gases (Andersen et al., 1999; Bush et al., 1998; Frederick et al., 1998; Teeguarden et al., 2008). In this type of model, inspiratory nasal airflow splits into dorsal and ventral components, with the dorsal flow passing over respiratory and olfactory compartments, and the ventral stream passing over respiratory compartments (Kimbell et al., 1997a). Multiple tissue stacks are comprised of mucus, epithelial, and submucosal compartments, all based on anatomical dimensions. Vapor transfer and clearance occurs by diffusion, metabolism, and blood perfusion at the appropriate epithelial levels. Morris and Hubbs (2009) also included the trachea which was divided into two equal-sized sequential stacks because responses from inhaled diacetyl were observed in the anterior and posterior trachea.

Inhalation of butter flavoring vapors has caused fixed airways obstruction in food manufacturing workers and has induced necrosis and inflammation of the nasal passages, larynx, trachea, and bronchi in exposed rats. Diacetyl, a primary ingredient of butter flavoring vapors, is thought to significantly contribute to airway injury and is therefore of particular concern. In a previous study, rats were exposed by inhalation to diacetyl concentrations of 100–356 ppm for 6 h (Hubbs et al., 2008). Dose dependent effects were observed in the nose, larynx, trachea, and bronchi, indicating high absorption rates in the upper respiratory tract and proximal lower respiratory tract. Although human occupational exposure also resulted in nasal irritation, more profound effects were observed in the lung, including the lower bronchial Airways. This represents a classical situation in risk assessment for highly soluble and reactive gases such as diacetyl: high solubility leads to high

¹ To whom correspondence should be addressed at The Hamner Institutes for Health Sciences, 6 Davis Drive, P.O. Box 12137, Research Triangle Park, NC 27709-2137. Fax: (919) 558-1300. E-mail: j Schroeter@thehamner.org.
nasal uptake in rats, and therefore most responses are observed in the nasal epithelium. The human nose, on the other hand, is much less efficient at filtering inhaled particles and gases, so higher concentrations are delivered to the lung airways, possibly presenting effects lower in the respiratory tract than can be observed in inhalation studies in rodents. For oral breathing in humans, this effect is even greater. Hubbs et al. (2008) state that “the shift in site of epithelial injury in the rat relative to the site of epithelial injury in diacetyl-exposed workers can be explained by known differences in rat and human respiratory tract anatomy with resulting changes in sites of vapor absorption.” The study by Morris and Hubbs (2009) uses simulation results to elucidate this problem.

Pathology data for inhaled diacetyl in exposed rats was analyzed in four standard nasal sections. Morris and Hubbs (2009) matched the locations of nasal sections with the corresponding compartments in the CFD-PBPK model to compare regional tissue dose with pathology scores. The approach used by these investigators to correlate localized tissue dose with regional pathology scores was pioneered by Kimbell et al. (1997b), where they correlated regional formaldehyde flux predictions from a nasal CFD model with formaldehyde-induced squamous metaplasia. A similar approach was subsequently used by Schroeter et al. (2008) to correlate regional acrolein flux predictions with acrolein-induced lesions in the olfactory region of the rat. In these latter two studies, CFD-based flux predictions around the perimeter of coronal cross-sections of the nose were compared with pathology data from corresponding histological sections. In all of these studies, excellent agreement was obtained between simulation results and pathology scores, showing that localized nasal responses induced by these soluble and reactive gases is directly related to tissue dose.

These investigators took these steps further by plotting regional pathology scores against predicted tissue concentrations in the four nasal sections and the trachea. The results collapsed into a single curve demonstrating a typical sigmoidal dose-response behavior. The fact that the data collapsed when plotted against regional tissue concentration as opposed to exposure concentration further shows that responses are directly due to localized tissue dose. From this data we can obtain a threshold tissue concentration that would lead to acute injury; in this case, it was estimated that responses would be seen for tissue concentrations exceeding 2mM. This value represents a tissue dose based no-observed-adverse-effect-level, meaning tissues that received concentrations less than 2mM would be predicted to be free of injury, whereas tissues receiving higher concentrations would be susceptible to injury. PBPK models for human inhalation can then be run over a wide range of exposure concentrations to evaluate the concentration level that would keep human nasal tissue concentrations below this threshold value, thereby obtaining human health risk levels based on quantitative tissue dose measures rather than default dosimetric adjustment factors.

Morris and Hubbs (2009) also demonstrated that diacetyl was metabolized in nasal tissues, presumably by diacetyl reductase. Because butyric acid is a potent inhibitor of diacetyl reductase, coexposure to butyric acid should lower overall absorption rates of diacetyl. This was shown from lower overall nasal uptake values by coexposure to these two compounds. This is important to consider when evaluating inhalation toxicity of butter flavoring vapors that contain both of these compounds because this would lead to lower absorption in the nose, allowing higher concentrations of diacetyl to penetrate to more sensitive lung airways, putting them at even greater risk of injury. Use of the CFD-PBPK model allows one to easily study coexposure effects and how different concentrations of butyric acid and metabolic reduction affect the local distribution of inhaled diacetyl.

In summary, these authors have demonstrated how a CFD-PBPK model can be used with other experimental techniques to describe inhalation dosimetry of inhaled diacetyl for quantitative risk assessment. Model parameters were calibrated with in vitro studies of diacetyl metabolism in nasal tissues, simulation results for nasal uptake were validated against in vivo uptake results in the isolated upper respiratory tract of exposed rats, and localized tissue concentrations were correlated with regional pathology scores from an inhalation exposure study. The latter two points demonstrate further confidence in the model predictions and suggest that regional tissue dose is a key contributor to respiratory responses following diacetyl exposure.

An underlying tenet of toxicology is that “the dose makes the poison,” yet the dose at sites where chemical-induced responses are observed is too often not determined in risk assessments. Instead, extrapolations are based on default assumptions of ventilation and anatomy and fail to take into account the vastly different dosimetry patterns that may occur between species. This study by Morris and Hubbs (2009) provides a general framework for how PBPK models can be used in quantitative risk assessments to correlate simulation results with regional pathology data from inhalation studies. These results can subsequently be extended to human models so that dosimetric relationships between species can be used for chemical safety evaluation.

REFERENCES


