

NOTICE: The copyright law of the United States (Title 17, U.S. Code) governs the making of photocopies or other reproductions of copyrighted material. Under certain conditions specified in the law, libraries and archives are authorized to furnish a photocopy or other reproduction. One of these specified conditions is that the photocopy or reproduction is not to be "used for any purpose other than private study, scholarship, or research."

The CDC library absorbs the cost of copyright fees charged by publishers when applicable and the cost of articles and books obtained from other libraries. **Copyright fees average \$35.00 and fees charged by the lending libraries are between \$10 and \$15 per request**

NASAL TISSUE DOSIMETRY—ISSUES AND APPROACHES FOR “CATEGORY 1” GASES: A Report on a Meeting Held in Research Triangle Park, NC, February 11–12, 1998

Melvin E. Andersen

Department of Environmental Health, Colorado State University,
Ft. Collins, Colorado, USA

Annie M. Jarabek

National Center for Environmental Assessment, Office of Research
and Development, U.S. Environmental Protection Agency, Research
Triangle Park, North Carolina, USA

Three organizations, the Basic Acrylic Monomer Manufacturers (BAMM), Methacrylate Producers Association (MPA), and Vinyl Acetate Toxicology Group (VATG), have sponsored development of physiologically based pharmacokinetic (PBPK) models for nasal tissue dosimetry with, respectively, acrylic acid (AA), methyl methacrylate (MMA), and vinyl acetate (VA). These compounds cause lesions in nasal epithelial tissues and are classified as “Category 1” gases within the U.S. EPA (1994) classification scheme. The National Center for Environmental Assessment in the U.S. EPA Office of Research and Development also has continuing interests in refining its methods for dosimetry adjustments when data on mode of action are available for Category 1 gases. A round-table discussion was held in Research Triangle Park, NC, on 11–12 February 1998, to develop a broader appreciation of the key processes and parameters required in developing nasal tissue dosimetry models. The discussions at the round table drew on these three case studies and several background presentations to assess the manner in which chemical-specific and mode-of-action data can be incorporated into nasal dosimetry models. The round table had representation from the U.S. EPA, academia, and industry. This article outlines the presentations and topical areas discussed at the round table and notes recommendations made by participants to extend models for nasal dosimetry and to develop improved data for modeling. The contributions of several disciplines—toxicology, engineering, and physiologically based pharmacokinetic (PBPK) modeling—were evident in the discussions. The integration of these disciplines in creating opportunities for dosimetry model applications in risk assessments has several advantages in the breadth of skills upon which to draw in model development. A disadvantage is in the need to provide venues and develop cross-discipline dialogue necessary to ensure the understanding of cultural attitudes, terminology, and methods. The round-table discussions were fruitful in achieving such enhanced understanding and communication. Subsequent elaboration of these models will benefit from the interactions of these groups at the round table. The

Received 18 December 2000; accepted 16 January 2000.

This article is not subject to U.S. copyright laws.

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.

Address correspondence to Dr. Melvin E. Andersen, Department of Environmental Health, Colorado State University, Ft. Collins, CO 80523, USA. E-mail: manders@cvmbs.colostate.edu

round-table discussions have already led to model improvements—as noted in several recently published articles. Participants emphasized several generic data needs in relation to nasal vapor uptake studies in human subjects, to broader discussion of tissue diffusion models, and to extensions to other classes of gases. The round-table articles that are published separately in this issue and the discussions, captured in this overview, provide a glimpse of the state of the science in nasal dosimetry modeling and a clear indication of the growth of and continuing opportunities in this important research area.

In recent years, there has been an increasing interest in applying dosimetry models to chemicals, in addition to the criteria air pollutants,* in order to estimate dose in various portions of the respiratory tract. These models have been developed to gain a better understanding of both the physiological and anatomical characteristics of animal species and the physico-chemical characteristics of specific inhaled materials that determine the amounts of gases absorbed by tissues in various regions of the respiratory tract. Two of the incentives for this work have been to derive a better characterization of the functions of the different regions of the respiratory tract and, in addition, to develop improved methods for assessing toxicity in each, ultimately supporting the regulation of potentially toxic substances in occupational and environmental situations. A major goal has been to extrapolate observations of toxicity and dosimetry in laboratory species to predict uptake and toxicity expected in human populations.

Dosimetry modeling efforts within the U.S. Environmental Protection Agency (EPA) aimed at the hazardous air pollutants (HAPs) have led to the development of the reference concentration (RfC) methods (U.S. EPA, 1994). According to the National Academy of Sciences (NAS) paradigm for risk assessment (NRC, 1983), the RfC is a dose-response estimate, defined as an estimate (with an uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious noncancer health effects during a lifetime (U.S. EPA, 1994). The RfC methods represent a watershed within the federal regulatory agencies. They specifically consider differences in dose to tissues between test animals and humans as part of the process for establishing dose-response estimates. The RfC is given by the following equation:

$$\text{RfC} = \frac{(\text{BMC or NOAEL}) \cdot \text{duration adjustment} \cdot \text{dosimetric adjustment factor (DAF)}}{\text{uncertainty factors} \cdot \text{modifying factor}}$$

*The Clean Air Act Amendments require that National Ambient Air Quality Standards (NAAQS) be set for any ubiquitous air pollutant that, if present in the air, may reasonably be anticipated to endanger the public health or welfare and whose presence in the air results from numerous or diverse mobile or stationary sources. The reference concentration (RfC) methods are not applied to develop dose-response assessments for these chemicals due to legislative requirements and major differences in the health databases for these pollutants. The RfC methods are used to perform dose-response assessment for air pollutants from point sources, such as the hazardous air pollutants (HAPs).

where BMC is a benchmark concentration and NOAEL is a no-observed-adverse-effect level. The dosimetric adjustment factor (DAF_r) varies for different regions of the respiratory tract versus remote (systemic effects), r , and for particles versus gases. The three regions of interest are the extra-thoracic, the tracheobronchial, and the pulmonary. Respiratory toxicologists typically delineate these areas because of differences in size, structure, function, and cell types.

Because the gases to which the RfC methods apply span such a broad range of available data, physicochemical characteristics, and toxicokinetic considerations,* no single model could be proposed in the RfC methods to characterize gas disposition in and toxicity to each of the three regions in the respiratory tract as well as remote sites (U.S. EPA, 1994). Instead, a category scheme was proposed so that model structures could be developed for limiting cases based on a general understanding of the determinants of uptake in the respiratory tract and a hierarchical approach that relied on a range of rich to rudimentary data. Category 1 gases are highly reactive or highly water-soluble and are expected to be deposited (absorbed) and have their toxic effects in the respiratory tract. Reactivity was used to denote the propensity to be metabolized, dissociate, or oxidize. Important considerations for distinguishing a limited model structure for this category of gases are that they are so reactive or soluble as to be “scrubbed” from the inhaled airstream and that this scrubbing results in a proximal to distal gradient (fractional penetration) of delivery and associated toxicity. They are also distinguished by the property that the gas does not accumulate in the bloodstream. Category 2 gases are less soluble and/or less reactive so that an accumulation of the chemical in the blood can result. Thus, these gases may have effects in either the respiratory tract or at remote (systemic) sites. Category 3 gases are even less water-soluble or reactive. These lipid-soluble gases readily reach the pulmonary region of the lungs, where they equilibrate across the alveolar membranes and distribute via arterial blood to the rest of the body to manifest systemic toxicity. Thus, this U.S. EPA categorization scheme encompasses broad considerations of the regions where the compounds cause their effects and their physicochemical characteristics. Similar schemes had been proposed by Dahl (1990), who characterized gases as stable, reactive, or metabolizable based on their thermodynamic and kinetic properties, and by the International Commission on Radiological Protection (1993). It must be noted that the categorization scheme is a continuum (U.S. EPA, 1994), and designation is a function of available information and subject to limitations in experimental techniques.

The formulation of the model structures used for the gas categories was based on consideration of existing structures that were also applied in a

*In fact, the inert gases that exert their effect by reversible “physical” interactions of gas molecules with biomolecules (e.g., “displacement” of oxygen by carbon monoxide) were not included in the categorization scheme and instead calculation of the maximum exposure concentration based on vapor pressure was recommended.

chemical- or class-specific fashion. Aharonson and colleagues (1974), using a typical chemical engineering approach, described the uptake of water-soluble and reactive gases (e.g., sulfur dioxide) in the nose on the basis of a mass-transport coefficient that captured bulk flow (convection), radial transport to the surface, solubility, and tissue reactivity. Resistance to transport is described relative to the various phases through which the mass of gas must travel, such as the air phase and the tissue phase. The geometry of the airways affects mass transfer in the air phase due to its influence on convection and surface area, and determines the distance over which a radial concentration gradient exists between the airflow and tissue. Diffusivity of the gas, a property of its molecular volume, affects the rate at which the gas is transported across the air-phase concentration gradient along the higher concentration in the air phase to the lower airphase concentration adjacent to the absorbing tissue. Solubility determines the tissue absorption capacity. Reactivity, including metabolism, increases the absorption capacity by depleting the absorbed mass of gas. By transforming the absorbed gas, reactivity also reduces tissue concentration, thereby increasing the tissue concentration gradient and the transport rate. The transport of heat has been described analogously, and Nuckols (1981) in fact used heat-transport studies in the nose to develop mass transfer coefficients to describe the air-phase transport rate.

Assuming the air-phase transport was of less significance than tissue transport for ozone in the lower airways, Miller et al. (1985) developed a distributed parameter model based on these same principles of mass transport for ozone deposition within the branching structures of the lower respiratory tract. This model, also described in several papers by Overton and colleagues (Overton, 1984; Miller et al., 1985; Overton et al., 1987; Overton & Miller, 1988; Overton & Graham, 1989), estimates the mass flux to the walls at different generations as the dose metric. The development of gas-phase mass-transport coefficients for the upper airways (Aharonson et al., 1974; Nuckols, 1981; Hanna & Scherer, 1986) allowed distributed parameter modeling of the entire respiratory tract (Morgan & Frank, 1977; Ultman, 1988; Hanna et al., 1989; Gerde & Dahl, 1991). Thus, the determinants of mass transport in the air and tissue phases formed the basis for the development of the U.S. EPA methods for assessing the "dose" of gases in the various regions of the respiratory tract for Category 1 gases. At the other end of the spectrum, Category 3 gases, different model structures had successfully been used to describe uptake of these lipid-soluble gases in the alveolar region and distribution to remote sites (Ramsey & Andersen, 1984). Because these gases are relatively insoluble in water and do not react with tissue, equilibrium between the gas and blood is established and the mass transport is dictated by the blood perfusion to the gas-exchange (alveolar) region.

The RfC methods also had to address the range of data available for the various gases and provided a hierarchal framework for designating optimal

versus default model structures and choice of dose metric (Jarabek, 1995). Optimal model structures demand a richer database to support mechanistic descriptions of gas uptake and target tissue interaction, requiring chemical- and species-specific parameters. The default approaches were aimed at more rudimentary descriptions, often using empirical fits to describe gas uptake and provide species-specific data, with the dose metric at a superficial level of detail. For example, the default for Category 1 gases invoked the assumption that the overall mass transfer coefficient would be high (by definition) in the nose and of similar magnitude in the laboratory animal and human. An overall dose to the upper respiratory tract (URT) was derived based on the fractional penetration of mass through that region; that is, mass absorbed within the region was calculated across the surface area of the region; that is, mass per time per surface area was used as the dose metric.

While this description was “correct” in terms of the geometry, airflow, and tissue-phase reactions being intact in the laboratory animal in which the mass transport was measured, the default was unsatisfying when substantial mechanistic data indicated that some other dose metric in a specific target tissue (e.g., amount of metabolite formed in the olfactory epithelium) would be more closely related to the toxicity. Such a hierarchal scheme for description of the dose metric is consistent with recent guidance on the consideration of the mode of action—defined as a chemical’s influence on molecular, cellular, and physiological functions in producing toxicity (*Federal Register*, 1996a). Optimal models would thus describe compound-specific mechanisms that extend consideration of the dose metric to the tissue phase as the basis for extrapolation from laboratory animals to humans. Even as the RfC methods were published (U.S. EPA, 1994), efforts were underway to develop compound-specific models for dosimetry in the URT that extended consideration of dose metrics to the tissue phase. This work included modeling with formaldehyde, vinyl acetate (VA), acrylic acid (AA), and methyl methacrylate (MMA), all of which were discussed at a round-table discussion entitled “Nasal Tissue Dosimetry—Issues and Approaches for ‘Category 1’ Gases,” held at Research Triangle Park, NC, on 11–12 February 1998.

THE SPEAKERS

The purpose of the round-table meeting was to develop a broader appreciation for the key processes and parameters required in nasal tissue dosimetry models. The discussions at the workshop drew on five background presentations and presentation of three case studies that outlined the manner in which mode-of-action data and chemical-specific information become incorporated into dosimetry models. These presentations were discussed in the context of the hierarchal framework. The hierarchy ranges from data-rich, chemical-specific models to sparser default models, such as the Category 1 gas default algorithm from the RfC methods. The progression, in relation to tissue dose, moves from a species- and compound-specific

dose metric associated with the mode of action for the chemical in localized tissue, to reduced forms such as the RfC default, which adjusts exposure concentration between species by a ratio of mass delivered per time to a regional respiratory tract surface. The round-table meeting covered a 2-day period in February 1998. On the first day, a number of background overviews relating to nasal tissue dosimetry were presented, including talks on computational fluid dynamics modeling for formaldehyde and on the general RfC framework. The evening of the first day was devoted to a poster session related to general concepts related to nasal dosimetry and demonstrations of the three specific dosimetry models developed for VA, AA, and MMA. The following section provides a brief outline of the topics of the individual presentations. With only one exception, the presenters have developed full articles that appear in this issue. The authors of each of the articles had made significant contributions to experimental methods for studying nasal function and toxicity, to approaches for evaluating deposition in the nose, and to nasal dosimetry modeling.

Background Presentations

Due to observations of carcinogenicity of formaldehyde in rodent inhalation bioassays in the late 1970s and early 1980s, an extensive body of work had accumulated on toxicity, biochemical toxicology, nasal deposition, and airway modeling with this compound. The body of research focused attention on the nasal anatomy, metabolic characteristics of epithelial cells within the nasal cavity, and airflow characteristics through the nasal passages (Morgan, 1991; Morgan et al., 1984, 1991; Mery et al., 1994). Among other benefits of this increased emphasis on nasal architecture, function, and toxicology were improved methods to evaluate toxicity in nasal tissues and standardization of histopathological nomenclature and evaluation of these tissues. Dr. Kevin Morgan, the lead-off speaker, on nasal tissue function, architecture, and toxicity, directed this activity at the CIIT.* Dr. Morgan discussed how consideration of physicochemical characteristics, airflow, tissue metabolism, and the spatial distribution of lesions provide insight into the relative roles of regional tissue dose and local tissue susceptibility in assessment of toxic responses to inhaled gases. Because the background information related to nasal structure and function has been discussed in detail elsewhere, no specific article on this topic was developed for this volume.

Dr. Julia Kimbell, a mathematician who was recruited to CIIT to apply engineering methods known as computational fluid dynamics (CFD) to describe airflow within the nose, accelerated the experimental work at CIIT. Dr. Kimbell outlined her work on computational approaches to airflow modeling in the nasal passages. These quantitative methods were important in determining relative distribution and velocity profiles of dominant lateral

*Formerly Chemical Industry Institute of Toxicology, now CIIT Centers for Health Research.

and medial airflow streams in the nose across laboratory species (rats and monkeys) and humans (Kimbell et al., 1993; Kepler et al., 1997; Subramaniam et al., 1998). These methods formed the basis for partitioning the airflow into local nasal regions with defined cell types and were used to extend the modeling into the tissue compartment for specific compounds presented in the case studies. The CFD work established that the flux of formaldehyde corresponded closely to the lesion distribution in the URT of rats. Recently these CFD results have been used to estimate the number of cells at risk based on the flux delivered to groups of cells. This parameter was required as input to the clonal growth model for rats and humans used to calculate a revised cancer risk of inhaled formaldehyde at CIIT (Kimbell et al., 1997; CIIT, 1999; Conolly et al., 2000).

Other advances in the 1980s included refinement and extension of the experimental methods used to measure deposition of gases from the airstream by the upper respiratory tract. Dr. John Morris from the University of Connecticut discussed experimental methods and PBPK models for nasal vapor deposition. He has developed techniques to measure removal of gases from the nose in anesthetized rats and applied these techniques to a wider variety of materials than had been done previously. These techniques permit evaluation of the effect of various parameters—airflow rate, blood perfusion rates, pretreatment with metabolic inhibitors, coexposure with irritants, and others—on nasal uptake of these gases. Dr. Morris also developed the first physiologically based pharmacokinetic (PBPK) model for uptake of gases by nasal tissues (Morris et al., 1993).

Dr. Linda Hanna, who developed mass transport models for soluble gas uptake in the respiratory tract using finite difference methods (Hanna & Scherer, 1986; Hanna et al., 1989) as well as empirically determined mass transport coefficients in the human upper airways, served as one of the principal authors of the U.S. EPA methods. Dr. Hanna presented the conceptual framework for the RfC methods (U.S. EPA, 1994). Her talk served to provide a primer on mass transport theory and also discussed how ongoing efforts such as those presented at the round table could be used to refine and extend the current default structures. For example, the work of Dr. Kimbell is being used to develop local mass-transport coefficients within the URT that correspond to specific sections used in histopathological evaluation of toxicity (Jarabek et al., 2001; Lou et al., 2001).

Another characteristic difference between the rodents used in the animal toxicity studies of these nasal toxicants and humans is characteristic differences in breathing patterns. Rodents are obligate nasal breathers, whereas the primates are oronasal breathers, with mouth breathing contributing more to total ventilation as breathing rate is increased (e.g., with exertion or exercise). Approximately 15% of the human population only breathes through the mouth regardless of the level of exertion (Niinimaa et al., 1981). This difference has led to a concern that important effects in deeper lung tissues in humans might not be observed in toxicological

studies with rodents and to question the relevance of nasal lesions to human health risk assessment (DeSesso, 1993). Proper dosimetric adjustment and consideration of mode of action in the target cell types are required to adequately address these concerns. Some toxicity studies with formaldehyde were conducted in rhesus monkeys to assess effects in the nose and in the trachea and upper airways (Monticello et al., 1989). As noted earlier, Dr. John Overton, U.S. Environmental Protection Agency, who provided this talk, has contributed extensively to modeling of vapor deposition throughout the respiratory tract and is another of the principal authors of the RfC methods. He discussed the issues involved in accounting for ventilation patterns and estimating dose to the lower respiratory tract for various gases in humans.

Case-Study Presentations

One of the surprises of the past 10 to 15 years has been the discovery that a relatively large number of diverse chemicals cause nasal epithelial toxicity. The groups of compounds include directly irritant compounds, such as formaldehyde and a number of organic acids, as well as compounds that are metabolized by enzymes within respiratory and olfactory epithelial tissues in the nose, such as organic esters (e.g., vinyl acetate and methyl methacrylate). Several of these compounds are commercially important monomers or commercially important as intermediates in various synthetic processes. A significant body of research has been conducted with several of these compounds, notably vinyl acetate (VA) (Bogdanffy et al., 1999) and acrylic acid (AA) (Frederick et al., 1998, and this issue), to assess dose response for target tissue toxicity, mode of action in vivo and in vitro, and nasal tissue metabolism. These various data have been integrated into models of tissue dosimetry that predict the delivery of inhaled compounds to target tissues in the nose. These dosimetry models have been employed to assess relative differences in dosimetry in laboratory rodents and in humans. In this way, these models address the dosimetric adjustment factor in the RfC equation above with a dose metric at a level of detail corresponding to the mechanism of toxicity within a specific tissue. Drs. Bogdanffy and Frederick discussed the data acquisition and modeling with these compounds. The emphasis in Dr. Bogdanffy's paper with VA was on the studies to define mode of action. The emphasis in Dr. Frederick's paper on AA was on the characteristics of model structure in relation to interspecies differences in predicted target tissue concentrations of AA within epithelial tissues in various regions of the nose.

There is always a fairly large investment in research required to develop the analytical tools and data to develop a convincing case that a particular dosimetry model has reliably captured the relevant information to calculate tissue dose for test and target species. When models are developed and validated for a specific compound or for a small group of compounds, it frequently becomes possible to extend the model structure to other com-

pounds using a much more limited research program. The model developed with MMA (Andersen et al., 1999) discussed by Dr. Andersen was developed based on a more limited data set, taking advantage of the insights and model structures developed with formaldehyde, VA, and AA.

Although the workshop was held in early 1998, several of the papers and modeling efforts were already accepted for publication, in revision, or in advanced draft form. As noted with some of the dates on the citations already for formaldehyde, VA, AA, and MMA, these articles are now available. Together with the compound-specific round-table articles and the background papers, the body of studies provides the interested reader with a glimpse of the development of these compound-specific models, their pedigree with respect to default models and earlier efforts, and their proposed use in establishing RfC values for these compounds.

INTERDISCIPLINARY INTERACTIONS AND TERMINOLOGY

The workshop was unusual in bringing together scientists from several diverse disciplines who study the uptake and toxicity of gases in nasal tissue. The overall magnitude of uptake in the nose is determined by several processes, any one of which can be rate-limiting for movement of compound from one region to another. In the nose, the main parameters that regulate uptake of chemical into tissues are gas flow, diffusion of compound in the air and liquid (tissue) phases, and the solubility and reactions in mucus and tissue. The concentration of gas in the nasal cavity has a proximal to distal gradient (i.e., fractional penetration) as the gas moves down the respiratory tract and from the airstream radially into the tissues. The development of nasal dosimetry modeling originated with chemical engineers comfortable with describing uptake using an overall mass-transfer coefficient (abbreviated K_g). In the models developed by Aharonson and colleagues (1974), convective flow through the nasal cavity influences radial mass transfer throughout the length of the nasal cavity.

An overall mass-transfer coefficient, K_g in the equation that follows, is comprised of individual terms containing mass-transfer coefficients for specific phases (symbolized as k_g terms) and solubility. For idealized cases, the overall mass-transfer coefficient can be represented as sums of resistances to transport in each of the different phases, air phase and tissue, such that:

$$1/K_g = 1/k_{g, \text{ gas}} + 1/(H_{v/a} \times k_{g, \text{ liquid}})$$

The first term is the resistance in the air phase. Hanna et al. (this issue) has emphasized that the gas-phase mass-transfer coefficients ($k_{g, \text{ gas}}$) depend on flow rates. The second term is the liquid-phase resistance in which tissue solubility expressed as the tissue:air partitioning, $H_{v/a}$, is explicitly included. Here, $H_{v/a}$ is the Henry's Law value of the gas. The liquid-phase resistance term includes a mass transport coefficient, $k_{g, \text{ liquid}}$, to define the diffusion

rate in the liquid phase. For reactive gases, this term also accounts for reaction or biotransformation rates (Ultman, 1988; U.S. EPA, 1994). Thus, the macroscopic (overall) K_g has contributions from diffusion, solubility, metabolism, and chemical reactions. When metabolism in the underlying mucus/tissue layer is via enzymatic reactions, absorption will vary with concentration and will become saturated as the tissue-phase concentrations become much greater than the affinity constants of the metabolizing enzymes.

The amount of gas removed during passage of the gas through the nasal cavities depends on diffusional mass transport, solubility and reaction rates expressed as the overall mass-transfer coefficient (K_g), the surface area of the region (SA), and airflow (Q). It must be emphasized that K_g is dependent on airflow. The fractional penetration (f_p) in any region in which the gas-phase concentration throughout the gas compartment is constantly diminishing with distance traveled is modeled using the K_g formulation by a simple differential equation described by Aharonson et al. (1974). Thus,

$$f_p = e^{-K_g SA/Q}$$

The extraction (E), that is, the proportion removed in the region, is 1.0 minus the fractional penetration:

$$E = 1 - e^{-K_g SA/Q}$$

The net uptake in any region is extraction times the airflow times the input concentration.

Empirically, K_g for this distributed parameter model structure could be estimated from the fractional penetration relationship based on experimental studies that provide information on the concentration of chemical exiting particular regions in the nose at various flow rates (Aharonson et al., 1974; Morris & Cavanagh, 1986; Hu et al., 1992). Alternatively, the transport resistances composing K_g can be determined separately and combined to obtain the absorption rate (U.S. EPA, 1994; Hanna et al., this issue). These models of mass transfer within the air phase and tissue phase account for continuous gradients of concentration as the gas moves through air and tissue compartments. In the more complicated geometry of the nose itself these gradients can be calculated either directly using computational fluid dynamics grids of the nose or with distributed parameter models. Approximations can be developed using models that contain multiple well-mixed compartments.

Several empirical studies have been performed to evaluate the gas-phase mass-transport coefficient (Nuckols, 1981; Hanna & Scherer, 1986; Lou, 1993; Hu et al., 1992; Ultman et al., 1994; Nodelman & Ultman, 1999a, 1999b). These coefficients are determined by establishing a known boundary condition, such as a concentration at the transport boundary. Recently, computational fluid dynamics (CFD) has been applied to deter-

mine airflow patterns in the nose and to calculate extraction of chemical within specific anatomical regions in rat or human noses to derive the gas-phase mass-transport coefficient (k_g). The CFD method solves the Navier-Stokes equations for fluid flow over a finite element model of the nasal cavity. Computationally, the tissue is assumed to act as an infinite sink, such that the concentration at the transport boundary is assumed to be zero. This condition is the so-called $C = 0$ boundary condition where the tissue concentration immediately adjacent to the air phase is assumed to be zero. Under these conditions, the overall mass-transfer coefficient is essentially equal to the gas-phase mass-transfer coefficient, since the tissue-phase transport is made irrelevant by this boundary condition. A difficulty in using CFD results to assess these gas-phase mass-transfer coefficients is in providing a description of the flow into individual air-phase regions. Air is not passed discretely from one region to the next. The flows move between and among regions, and the assignment of flows to regions varies with flow rate. In addition, the estimation of these gas-phase mass-transfer coefficients with the $C = 0$ boundary condition has to be done with air-phase concentrations that permit accurate estimation of wall fluxes throughout each of the air-phase compartments.

Scientists with backgrounds in a third area, physiologically based pharmacokinetic (PBPK) modeling, have also applied methods from this discipline to evaluate nasal uptake of inhaled gases. In this approach the nasal cavity and adjacent tissues are broken down into a series of specific air and tissue compartments (see Morris et al., 1993). Similar to the manner in which distributed parameter models address reaction processes such as dissociation and oxidation, PBPK models can be used to incorporate biochemical parameters for metabolism within specific tissue compartments. In these PBPK models, the concentration in each compartment is given by a single value. The model assumption is that the diminishing concentration (both proximal to distal and radially from the air phase to tissue) within the nasal cavity as the gas is absorbed can be modeled using a series of well-mixed compartments.

In the first PBPK models developed for the nose, the mucus and air compartments were in equilibrium in each of the individual regions within the nose (Morris et al., 1993; Plowchalk et al., 1997). This assumption is only valid when the overall mass-transfer rate is determined by the tissue phase alone, that is, when reactions (either physicochemical or metabolic) in the tissue phase are so low as to have the tissue phase resistance control absorption. Under these conditions, the concentration in the central air-stream is equal to the concentration at the transport (or tissue) boundary. Highly reactive (Category 1) gases and some Category 2 gases (e.g., sulfur dioxide or ozone) manifest an air-phase gradient. Under these conditions, the uptake into the tissues is controlled either by the air phase or by both the air phase and tissue phase contributing to the transport resistance. To enlarge the utility of these nasal PBPK models it was necessary to develop

methods to account for cases where air-phase mass transport could be contributing to the transport resistance.

Thus, a difficult challenge in enlarging these PBPK models was to incorporate the mass-transport resistance within the air phase and the manner in which airflow through the nasal passages determine the air-phase limitations on nasal uptake. Frederick and colleagues (1998), using the results from CFD modeling of the rat nose, provided the insight to solve this problem. The net extraction from a particular region of the nose was calculated from the CFD solutions for specific nasal geometries and specific flow rates assuming the $C = 0$ boundary condition. The extraction noted with a $C = 0$ boundary condition in the CFD calculations is related to the specific flow rate and air-phase diffusion. Simple considerations from the PBPK model structure with well-mixed air-phase compartments show that the maximum extraction at a fixed flow rate with the $C = 0$ boundary condition is related to the ratio of air-phase diffusion, that is, the gas-phase mass-transport coefficient derived by the CFD modeling, divided by the sum of this air-phase diffusion term and the airflow rate.

$$\text{Extraction} = PA_{\text{gas}} / (Q + PA_{\text{gas}})$$

The air-phase diffusion term in this equation is PA_{gas} . The regional extraction predicted at a specific flow rate from the $C = 0$ boundary condition in CFD modeling was used to derive PA_{gas} at that flow rate for the individual nasal regions. The case studies with VA, AA, and MMA reported in this workshop have taken advantage of this insight in formulating equations for the individual air phase compartments in the PBPK models. In this formulation, the PA_{gas} term is equated to the product of the surface area times an effective mass-transfer coefficient in the air phase (" $k_{\text{g,eff}}$," derived for a well-mixed compartment geometry (Frederick et al., 1998). Thus,

$$PA_{\text{gas}} = "k_{\text{g,eff}}" SA$$

The value of the air-phase mass-transfer coefficient (k_{g}) used in the engineering applications and developed empirically or computationally using CFD differs from that derived for these PBPK models (" $k_{\text{g,eff}}$ "). The former is based on a distributed air phase, while the latter uses a description based on a well-mixed air-phase compartment. Although this is not provided in the workshop paper, Andersen and Sarangapani (1999) calculated the relationship of these two different representations of the mass-transfer coefficient for the air phase. The relationship, which represents the generalized case for compartmental approaches at a fixed flow rate, is based on expressing both the distributed model k_{g} and the well-mixed air-phase model " $k_{\text{g,eff}}$ " in terms of the E_{cfd} , the extraction calculated from the CFD modeling.

$$k_{\text{g}} = -Q \ln(1 - E_{\text{cfd}}) / SA \quad \text{and} \quad "k_{\text{g,eff}}" = E_{\text{cfd}} Q / (1 - E_{\text{cfd}}) / SA$$

Thus,

$$"k_{g,\text{eff}}" = k_g[-E_{\text{cfid}}/(1 - E_{\text{cfid}})/\ln(1 - E_{\text{cfid}})]$$

The two values k_g and " $k_{g,\text{eff}}$ " are similar for regions of low extraction and diverge more and more for high-extraction behaviors. This relationship can be used to derive the well-mixed air-phase mass-transfer coefficient from the CFD results at each flow rate to match similar extraction patterns, depending on the model structure for the air-phase compartments. The difference between these two model-derived values for the air-phase mass-transfer coefficient derives in part from the well-mixed compartment description in the PBPK models versus the more realistic descriptions of gradients of concentrations in the distributed models. The air-phase concentration in the PBPK models is given by a single value, and the concentration throughout the compartment is assumed to be the same as the exiting concentration.

It is also important to stress that the relationships developed in these equations relating extraction, PA_{gas} , and airflow provide parameters appropriate for the particular flow rate. The PA_{gas} estimated in this fashion for the PBPK modeling approach, is dependent on airflow and should not be regarded as a constant. In practice, PA_{gas} must be estimated from extraction estimates from CFD calculations for all the flow rates of interest.

Since the early 1970s, study of removal of drugs from blood by specific organs has relied on two concepts. One is extraction and the other is clearance. Extraction is the proportion of chemical removed from the blood during passage through the tissue. Clearance (volume/time) is the net volumetric flow from which chemical was removed. Clearance is very useful as a proportionality factor. Input concentration times clearance equals the net amount of chemical removed by the organ. Clearance and extraction can also be applied to describe removal of compounds from the airstream by the nose. They can be applied when using either type of modeling, that is, the well-mixed air compartments or the distributed air-phase formulations.

For the case with well-mixed air-phase compartments, Andersen and Sarangapani (1999) developed equations describing the relationship of steady-state nasal clearance of gases (Cl_{nose}) from the airstream to individual flow, diffusion, and metabolism terms expressed as a series of reciprocals.

$$1/Cl_{\text{nose}} = 1/(H_{\text{m:a}} Cl_{\text{tissue}}) + 1/(PA_{\text{gas}}) + 1/Q$$

In this relationship, the Cl_{tissue} term includes both liquid-phase diffusion and metabolism of the gas in the tissues. In addition, both airflow (Q) and gas-phase diffusional clearances (PA_{gas}) are explicitly included in this relationship and, since PA_{gas} is specific to the flow rate used in the CFD model, both terms should be considered flow-rate dependent. Dividing these clearance, PA , and flow terms by the surface area, the equation becomes similar to that for the overall mass-transfer coefficient used in the engineering

approach as shown in the earlier equation. In this case, the values for the air-phase mass-transfer coefficient in the two formulations differ as noted earlier.

The differences in these coefficients between the mass transport and hybrid PBPK clearance approaches become important when attempting to model acute exposures (i.e., when not at steady state or for cyclical breathing) and in extrapolating to other flow rates, such as when adjusting a ventilation rate for different body weights within a species (e.g., F344 to SD rat) and especially when considering ventilation for different activity patterns in humans (e.g., resting vs. exertion levels for various time periods). Hanna et al. (this issue) have developed a generalized relationship that could be used to estimate clearance for a variety of flow rates and activity patterns:

$$Cl = \dot{V}_e E = \dot{V}_e (1 - e^{-K_g/SA/\dot{V}_e}) = \dot{V}_e (1 - f_p)$$

where V_e is the minute ventilation, or can be the inspired volumetric flow and equivalent to Q in the PBPK descriptions noted earlier.

Although the nomenclature of the distributed parameter models using the mass-transport coefficient approach differs from that of the PBPK modeling approach, the models describe similar processes. As noted earlier, the clearance and mass-transfer formulations can be provided in a manner to highlight their underlying similarities. In most of the older engineering-related literature, *absorption rate* and *fractional penetration* are terms used to describe the loss of compound in the nose or the proportion of compound that exits the nose. In contrast, the pharmacokinetic literature regarding loss of compounds during passage of blood through an organ uses *clearance* and *extraction* terms. Because clearance is the volumetric flow from which the compound is removed, extraction is also given by clearance divided by a specific total flow through any region. Either of these descriptions, that preferred in the engineering literature or that more common to the pharmacokinetic literature, with their distinct nomenclature, can be applied to studies of the loss of compounds from the airstream as they pass through the nose. It is not so important that nasal modeling follow the traditions of any single discipline. It is much more important that practitioners from the various disciplines make efforts to appreciate and understand the contributions and approaches offered by other disciplines and that scientists from all fields make efforts to properly validate the predictions of specific models.

GENERAL ROUND-TABLE DISCUSSIONS

The round table provided an opportunity to appreciate the background research and interdisciplinary contributions that have led to the application of nasal dosimetry models for Category 1 gases in contemporary risk assess-

ments. The seminal contributions of the U.S. EPA reference concentration (RfC) methods in establishing a uniform role of dosimetry modeling in risk assessment were noted to be a critical turning point in the use of dosimetry models in risk assessment with inhaled materials. The RfC process established a framework that could be applied to a range of gases that affected various portions of the respiratory tract or that had systemic effects. Data availability was also a key consideration. Default models used a limited number of parameters and defined measures of average deposition rates in various regions of the respiratory tract as the dose metric for interspecies comparison. These default models are applicable when specific data for a test compound are scanty or nonexistent. The applications of dosimetry models with the four specific compounds, formaldehyde, VA, AA, and MMA, represent the extension of these basic modeling concepts to establish dose measures that are based more directly on presumed modes of action in the target tissues.

Category 1 gases and vapors are those that have high solubility or reactivity or both, such that they are likely to be removed with a proximal to distal distribution in the respiratory tract. Of the three compounds described in detail (excluding formaldehyde), AA comes closest to fulfilling these criteria. Its high uptake is due to rapid ionization in tissues at biological pH, resulting in high partitioning into the proximal tissues. VA is also highly extracted by nasal tissues at low concentrations; total nasal extraction of VA is dose dependent, decreasing with increasing inhaled concentrations. The extraction in this case is related to metabolism mediated by carboxylesterases. In contrast, although MMA has effects in the nose, it is not highly extracted. Thus, MMA is neither highly soluble nor highly reactive. It can be regarded as a Category 1 vapor for the purposes of deriving a chronic risk estimate more on the basis of its site of action than on the basis of its physicochemical characteristics.

Another difference among these models is in relation to the dose metric used for the risk assessments. Obviously, the dose metric chosen depends on the known or presumed mode(s) of action of a compound in causing nasal effects. The dose metrics in the various case-specific models were flux to specific surface areas (formaldehyde); target tissue concentration of AA; target tissue concentration of hydrogen ion for VA; and the rate of metabolism of MMA to methacrylic acid divided by the target tissue compartment volume for MMA. Each of the dose metrics, equated with or derived from net flux into tissue, estimates an effective concentration of toxic compound at a target site in the nasal epithelium. In general, it may be best to provide a series of tissue dose metrics, as done by Bogdanffy et al. (1999), and discuss the merits of each. For calculating AA concentration and pH calculations, the AA and VA models include formation or delivery by diffusion and the elimination of toxic compounds from the tissue. The VA model also includes control of hydrogen ion by specific tissue buffers and hydrogen transporter systems. These models have more bio-

logical plausibility; they also require more extensive experimental work for validation. The MMA model is sparser. The dose metric depends on MMA diffusion into the target tissue compartments and on hydrolysis in those compartments to methacrylic acid. A compelling question, as the complexity of these dosimetry models increases, is how convincing these models are in calculating specific measures of dose. In addition, they raise important questions about the nature of the dose metric that should be used in assessing toxicity in the nasal tissues and about the reliability of various measurement techniques and extension to different conditions (e.g., cyclic flow vs. steady state).

The default dose metric for Category 1 gases is flux across a regional surface area. If all other processes in the tissues were linear, the expectation would be that tissue concentrations and fluxes would be proportional. This is likely the case at low levels associated with no-observed-adverse-effect levels. For formaldehyde, a very reactive gas, flux has served as a direct dose metric to a clonal growth model that accounts for nonlinear tissue interactions. For the three other examples, the tissue dosimetry models are nonlinear due to saturation of metabolism with VA and MMA and due to pH-dependent partitioning of AA. The default use of a flux as a dose measure is valuable for generic cases. As modes of action are developed, the need arises to calculate more specific measures of tissue dose, as with these examples. In the longer term, these models also lead to specific predictions about distribution of doses within the respiratory-tract tissues that might be tested by new experimentation with respect to concentration gradients in tissues or pH in specific regions of the nasal epithelium. Development of a suite of case-specific nasal dosimetry models may provide opportunities to establish various defaults based on modes of action or class of inhaled compounds. In fact, the concept of suites of different model structures is being used by the U.S. EPA and other agencies to provide the flexibility required to address the range of data available on the physicochemical properties and mode of action for a compound (Jarabek, 2000).

The compound-specific models for VA, AA, and MMA indicate that the default interspecies adjustment based on flux was likely to be conservative for these compounds. However, the reasons for these interspecies differences differ for the individual compounds. Interspecies differences with VA and MMA are related to a large extent by the localization and relative concentration of carboxylesterases in rodent and in human nasal tissues. With AA, the tissue concentrations largely reflect the inhaled concentrations, leading to a near equivalence across species. In all cases, the dose-dependent model behaviors are complicated and have been unraveled by sensitivity analyses conducted as part of the modeling process (Plowchalk et al., 1997; Andersen et al., 1999) or at a later stage of model analysis (Andersen et al., 2000). These sensitivity analyses have helped understand the nonlinear characteristics of these three models and indicated optimal areas of

research investments. The workshop participants noted the important role of sensitivity analysis in assessing model behavior and evaluating the relative importance of various model parameters.

Another area of interest noted by the participants was in attempting to define the optimal model structure required for accurate calculation of tissue doses. The different models range from creation of multiple grid points with many individual compartments or bins, as done recently with formaldehyde, to the use of a small number of nasal regions, three to seven in the PBPK models described here, with a variable number of underlying tissue compartments. A one-compartment nasal model is also described in the contribution to the round table (Frederick et al., this issue). Simulation of these different models with different assumptions regarding the tissue structures, as done in work by Bush et al. (1998), should be important in determining the minimal number of tissue compartments necessary to provide an adequate dosimetry model for risk assessment purposes.

SUGGESTED DATA NEEDS

The era of development and use of dosimetry models in a variety of risk assessments has dawned. (We would like to call this “The 2001 Toxicology Odyssey.”) The RfC documentation with a clear framework for routine consideration of tissue dosimetry has broken new ground. In addition, applications of compound-specific dosimetry models are becoming more widespread: for RfC calculations (U.S. EPA, 1994), in case studies for the new cancer guidelines (ILSI, 1997), and in route-to-route extrapolations involved with the proposed Hazardous Air Pollutants (HAPs) Test Rule (*Federal Register*, 1996b). The IRIS assessments for ethylene glycol monobutyl ether (U.S. EPA, 1999) and vinyl chloride (U.S. EPA, 2000) have made use of PBPK models for standard setting and route-to-route extrapolation. OSHA standard setting with methylene chloride has made use of a PBPK model for tissue dosimetry of metabolites (OSHA, 1997). The confident use of these dosimetry models will require continuing attention to collection of compound-specific data and to considerations of confirmation of predicted rodent human differences by limited experimentation in human subjects. One area of fruitful study emphasized in the round-table discussions for the nasal dosimetry models is the collection of uptake data for humans—both with specific test chemicals and with compounds selected due to their metabolic, solubility, or toxic properties. In limited number, human uptake studies have been conducted using various designs for breathing patterns and sampling. They include oral inspiration with either oral or nasal exhalation (Nodelman & Ultman, 1999a, 1999b).

Anatomic and physiologic parameters in the various species used in risk assessment were also acknowledged as a data gap. Further development of methods to measure parent compounds, metabolites, and dose metrics, such as pH, directly in nasal tissues will be important for validat-

ing these various dosimetry models. Such data are required to have confidence in calculations of concentrations in various target tissues or in the number of cells at risk (Kohn, 1997; CIIT, 1999).

Different models apply different approaches for handling the gas and liquid (tissue) phase diffusivities. Further research into the optimal model structures and the calculation of these diffusivity constants should be helpful in establishing improved models of the tissue regions within the nasal epithelial tissues. Continuing studies in laboratory animals should be pursued to enlarge the classes of chemicals examined in regard to uptake, reactivity, and toxicity. These might include organic compounds metabolized by cytochrome P-450 enzymes within nasal epithelial tissues, such as styrene and chloroform. In addition, pharmacodynamic characteristics such as recovery and repair need to be considered eventually in establishing differences between test animals and humans. Studies of tissue accumulation of metabolites in various nasal regions will also be helpful in establishing target tissue concentrations in respiratory and olfactory epithelia within the nose and in validating these dosimetry models.

SUMMARY

This round table provided a timely opportunity to assess the status of nasal dosimetry models for both generic and for case-specific applications. The attendees were optimistic about the application of these models for risk evaluations for a variety of compounds that affect nasal epithelial tissues. Great strides have been made in joining the talents and energies of scientists from diverse disciplines in improving estimation of tissue dose and use of this data in risk assessments. Obviously, the collection of specific new data will aid in developing confidence in the interspecies extrapolation from the increasingly robust animal data sets on dosimetry and mode of action. The models with formaldehyde, VA, and AA highlight the integration of large mechanistic data sets in a risk assessment context. The modeling with MMA represents a more minimalistic approach that takes advantage of the investments in model development with the other compounds to create a useful model with a smaller base of data. The issues noted for further experimentation—on human uptake, tissue- and gas-phase diffusion, extension to other classes of compounds, and so on—do not detract from the advances made in establishing important default procedures and in providing case-specific models with the four chemicals. Importantly, the lessons learned in developing dosimetry models for reactive gases, organic esters, and acids should be readily extended to other compounds with similar properties.

REFERENCES

- Aharonson, E. F., Menkes, H., Gurtner, G., Swift, D. L., and Proctor, D. F. 1974. Effect of respiratory airflow rate on removal of soluble vapors by the nose. *J. Appl. Physiol.* 37:654-657.

- Andersen, M. E., and Sarangapani, R. 1999. Clearance concepts applied to the metabolism of inhaled vapors in tissues lining the nasal cavity. *Inhal. Toxicol.* 11:873–897.
- Andersen, M. E., Sarangapani, R., Frederick, C. B., and Kimbell, J. S. 1999. Dosimetric adjustment factors for methylmethacrylate derived from a steady-state analysis of a physiologically based clearance–extraction model. *Inhal. Toxicol.* 11:899–926.
- Andersen, M. E., Sarangapani, R., Gentry, P. R., Clewell, H. J. III, Covington, T. R., and Frederick, C. B. 2000. Application of a hybrid CFD-PBPK nasal dosimetry in an inhalation risk assessment: An example with acrylic acid. *Toxicol. Sci.* 57:312–325.
- Bogdanffy, M. S., Sarangapani, R., Plowchalk, D. R., Jarabek, A. M., and Andersen, M. E. 1999. A biologically-based risk assessment for vinyl acetate-induced cancer and noncancer inhalation toxicity. *Toxicol. Sci.* 51:19–35.
- Bush, M. L., Frederick, C. B., Kimbell, J. S., and Ultman, J. S. 1998. A CFD-PBPK hybrid model for simulating gas and vapor uptake in the rat nose. *Toxicol. Appl. Pharmacol.* 150:133–145.
- CIIT. 1999. Formaldehyde: Hazard Characterization and Dose-Response Assessment for Carcinogenicity by the Route of Inhalation, rev. ed. 28 September, Research Triangle Park, NC.
- Conolly, R. B., Lilly, P. D., and Kimbell, J. S. 2000. Simulation modeling of the tissue disposition of formaldehyde to predict nasal DNA–protein crosslinks in Fischer 344 rats, rhesus monkeys, and humans. *Environ. Health Perspect.* 108(suppl. 5):919–924.
- Dahl, A. R. 1990. Dose concepts for inhaled vapors and gases. *Toxicol. Appl. Pharmacol.* 103:185–197.
- DeSesso, J. M. 1993. The relevance to humans of animal models for inhalation studies for cancer in the nose and upper airways. *Qual. Assur. (San Diego)* 2:213–231.
- Federal Register. 1996a. Proposed guidelines for carcinogen risk assessment: Notice of availability and opportunity to comment. 61:17960–18011.
- Federal Register. 1996b. Part II Environmental Protection Agency. 40 CFR 799. Proposed test rule for hazardous air pollutants; Proposed Rule. *Fed. Reg.* (61 FR 33178) June 26, 1996, as amended on December 24, 1997 (62 FR 67466) and on April 21, 1998 (63 FR 19694).
- Frederick, C., Bush, M. L., Subramaniam, R. P., Black, K. A., Finch, L., Kimbell, J. S., Morgan, K. T., Subramaniam, R. P., Morris, J. B., and Ultman, J. S. 1998. Application of a hybrid computational fluid dynamics and physiologically based inhalation model for interspecies dosimetry extrapolation of acidic vapors in the upper airways. *Toxicol. Appl. Pharmacol.* 152:211–231.
- Freidman, M. H. 1986. *Principles and modeling of biological transport*. Berlin: Springer-Verlag.
- Gerde, P., and Dahl, A. R. 1991. A model for the uptake of inhaled vapors in the nose of the dog during cyclic breathing. *Toxicol. Appl. Pharmacol.* 109:276–288.
- Hanna, L. M., and Scherer, P. W. 1986. Measurement of local mass transport coefficients in a cast model of the human upper respiratory tract. *J. Biochem. Eng.* 108:12–18.
- Hanna, L. M., Frank, R., and Scherer, P. W. 1989. Absorption of soluble gases and vapors in the respiratory system. In *Respiratory physiology: An analytical approach*, eds. H. K. Chang and M. Paiva, pp. 277–316. New York: Marcel Dekker.
- Hu, S. C., Ben-Jebria, A., and Ultman, J. S. 1992. Longitudinal distribution of ozone absorption in the lung: Quiet respiration in healthy subjects. *J. Appl. Physiol.* 73:1655–1667.
- International Commission on Radiological Protection. 1993. Gases and vapours. In *Human respiratory tract model for radiological protection: A report of Committee 2 of the International Commission on Radiological Protection*, pp. 57–66. Sutton, Surrey, UK: International Commission on Radiological Protection.
- International Life Sciences Institute. 1997. An Evaluation of EPA's Proposed Guidelines for Carcinogen Risk Assessment Using Chloroform and Dichloroacetic Acid as Case Studies: Report of an Expert Panel. Washington, DC: International Life Sciences Institute, Health and Environmental Sciences Institute.
- Jarabek, A. M. 1995. The application of dosimetry models to identify key processes and parameters for default dose-response assessment approaches. *Toxicol. Lett.* 79:171–184.
- Jarabek, A. M. 2000. Mode of action: Framework for dosimetry model development. Presented in *Mode-of-Action Dosimetry: An interagency project to develop models for inhalation, oral and dermal disposition*. Annual meeting of the Society for Risk Analysis, 4–6 December, Arlington, VA.

- Jarabek, A. M., Kimbell, J. S., Schlosser, P. M., Lou, S.-R., and Hanna, L. M. 2001. Computational fluid dynamics and mass transport calculations update the inhalation reference concentration methods: Rat. Abstract accepted for presentation at the 40th Annual Meeting of the Society for Toxicology, 25–29 March.
- Kepler, G. M., Richardson, R. B., Morgan, K. T., and Kimbell, J. S. 1997. Computer simulation of inspiratory airflow and inhaled gas uptake in a rhesus monkey. *Toxicol. Appl. Pharmacol.* 150: 1–11.
- Kimbell, J. S., Gross, E. A., Joyner, D. R., Godo, M. N., and Morgan, K. T. 1993. Application of computational fluid dynamics to regional dosimetry of inhaled chemicals in the upper respiratory tract of the rat. *Toxicol. Appl. Pharmacol.* 121:253–263.
- Kimbell, J. S., Gross, E. A., Richardson, R. B., Conolly R. B., and Morgan, K. T. 1997. Correlation of regional formaldehyde flux predictions with the distribution of formaldehyde-induced squamous metaplasia in F344 rat nasal passages. *Mutat. Res.* 380:143–154.
- Kohn, M. C. 1997. The importance of anatomical realism for validation of physiological models of disposition of inhaled toxicants. *Toxicol. Appl. Pharmacol.* 147:448–458.
- Lou, S.-R. 1993. Modeling of gas absorption: Upper airway scrubbing. Dissertation, Baltimore, MD: The Johns Hopkins University.
- Lou, S.-R., Kimbell, J. S., Jarabek, A. M., Schlosser, P. M., and Hanna, L. M. 2001. Computational fluid dynamics and mass transport calculations update the reference concentration methods: Human. Abstract accepted for presentation at the 40th Annual Meeting of the Society for Toxicology, 25–29 March.
- Mery, S., Gross, E. A., Joyner, D. R., Godo, M., and Morgan, K. T. 1994. Nasal diagrams: A tool for recording the distribution of lesions in rats and mice. *Toxicol. Pathol.* 22:353–372.
- Miller, F. J., Overton, J. H., Jaskot, R. H., and Menzel, D. B. 1985. A model of the sensitivity of the regional uptake of gaseous pollutants in the lung. I. The sensitivity of the uptake of ozone in the human lung to lower respiratory tract secretions and to exercise. *Toxicol. Appl. Pharmacol.* 79: 11–27.
- Monticello, T. M., Morgan, K. T., Everitt, J. I., and Popp, J. A. 1989. Effects of formaldehyde gas on the respiratory tract of rhesus monkeys: Pathology and cell proliferation. *Am. J. Pathol.* 134: 515–527.
- Morgan, K. T. 1991. Approaches to the identification and recording of nasal lesions in toxicology studies. *Toxicol. Pathol.* 19:337–351.
- Morgan, M. S., and Frank, R. 1977. Update of pollutant gases by the respiratory system. In *Respiratory defense mechanisms: Part I*, eds. J. D. Brain, D. F. Proctor, and L. M. Reid, pp. 157–189. New York: Marcel Dekker.
- Morgan, K. T., Jiang, X.-Z., Patterson, D. L., and Gross, E. A. 1984. The nasal mucociliary apparatus: Correlation of structure and function in the rat. *Am. Rev. Respir. Dis.* 130:275–281.
- Morgan, K. T., Kimbell, J. S., Monticello, T. M., Patra, A. L., and Fleishman, A. L. 1991. Studies of inspiratory airflow patterns in the nasal passages of the F344 rat and rhesus monkey using nasal molds: Relevance to formaldehyde toxicity. *Toxicol. Appl. Pharmacol.* 110:223–240.
- Morris, J., and Cavanagh, D. 1986. Deposition of ethanol and acetone vapors in the upper respiratory tract of the rat. *Fundam. Appl. Toxicol.* 6:78–88.
- Morris, J. B., Hassett, D. N., and Blanchard, K. T. 1993. A physiologically based pharmacokinetic model for nasal uptake and metabolism of nonreactive vapors. *Toxicol. Appl. Pharmacol.* 123: 120–129.
- National Research Council. 1983. *Risk assessment in the federal government: Managing the process*. Washington, DC: National Academy Press.
- Niinimaa, V., Cole, P., Mintz, S., and Shepard, R. J. 1981. Oronasal distribution of respiratory airflow. *Respir. Physiol.* 43:69–75.
- Nodelman, V., and Ultman, J. S. 1999a. Longitudinal distribution of chlorine absorption in human airways: A comparison to ozone absorption. *J. Appl. Physiol.* 87(6):2073–2080.
- Nodelman, V., and Ultman, J. S. 1999b. Longitudinal distribution of chlorine absorption in human airways: Comparison of nasal and oral quiet breathing. *J. Appl. Physiol.* 86(6):1984–1993.

- Nuckols, M. L. 1981. Heat and Water Vapor Transfer in the Human Respiratory System at Hyperbaric Conditions. Naval Coastal Systems Center Tech. Rep. No. TR364-81.
- Occupational Safety and Health Administration. 1997. Occupational exposure to methylene chloride; Final rule. *Fed. Reg.* 62(7):1493-1619.
- Overton, J. H., Jr. 1984. Physicochemical processes and the formulation of dosimetry models. In *Fundamentals of extrapolation modeling of inhaled toxicants: Ozone and nitrogen dioxide*, eds. F. J. Miller and D. B. Menzel, pp. 93-114. Washington, DC: Hemisphere.
- Overton, J. H., and Graham, R. C. 1989. Predictions of ozone absorption in human lungs from newborns to adult. *Health Phys.* 57(suppl. 1):29-36.
- Overton, J. H., and F. J. Miller. 1988. Dosimetry modeling of inhaled toxic reactive gases. In *Air pollution, the automobile, and public health*, eds. A. Y. Watson, R. R. Bates, and D. Kennedy, pp. 367-385. Washington, DC: National Academy Press.
- Overton, J. H., Graham, R. C., and Miller, F. J. 1987. A model of the regional uptake of gaseous pollutants in the lung: II. The sensitivity of ozone uptake in laboratory and animal lungs to anatomical and ventilatory parameters. *Toxicol. Appl. Pharmacol.* 88:418-432.
- Plowchalk, D. R., Andersen, M. E., and Bogdanffy, M. S. 1997. Physiologically-based modeling of vinyl acetate uptake, metabolism, and intracellular pH changes in the rat nasal cavity. *Toxicol. Appl. Pharmacol.* 142:386-400.
- Ramsey, J. C., and Andersen, M. E. 1984. A physiologically-based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol. Appl. Pharmacol.* 73:159-175.
- Subramaniam, R. V., Richardson, R. B., Morgan, K. T., and Kimbell, J. S. 1998. Computational fluid dynamics simulations of inspiratory airflow in the human nose and nasopharynx. *Inhal. Toxicol.* 10:91-120.
- Ultman, J. S. 1988. Transport and uptake of inhaled gases. In *Air pollution, the automobile, and public health*, eds. A. Y. Watson, R. R. Bates, D. Kennedy, pp. 232-366. Washington, DC: National Academy Press.
- Ultman, J. S., Ben-Jebria, A., and Hu, S. 1994. Noninvasive Determination of Respiratory Ozone Absorption: The Bolus-Response Method. Research Rep. No. 69. Cambridge, MA: Health Effects Institute.
- U.S. Environmental Protection Agency. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. EPA/600/8-90/066F. Office of Research and Development, National Center for Environmental Assessment, Research Triangle Park, NC. October.
- U.S. Environmental Protection Agency. 1999. Toxicological Review of Ethylene Glycol Monobutyl Ether (EGBE). EPA/635/R-00/002. Integrated Risk Information System (IRIS) <<http://www.epa.gov/iris>>. National Center for Environmental Assessment, Washington, DC.
- U.S. Environmental Protection Agency. 2000. Toxicological Review of Vinyl Chloride. Appendices A-D. EPA/635R-00/004. Integrated Risk Information System (IRIS) <<http://www.epa.gov/iris>>. National Center for Environmental Assessment, Washington, DC.