Development of a Physiologically Based Pharmacokinetic Model of Isopropanol and Its Metabolite Acetone

Harvey J. Clewell, III,* † P. Robinan Gentry,* Jeffery M. Gearhart, ‡ Tammy R. Covington,* Marcy I. Banton,‡ and Melvin E. Andersen§

*The K. S. Crump Group, Inc., ICF Consulting, 602 East Georgia Avenue, Ruston, Louisiana 71270; † ManTech Environmental Technology, Inc., Dayton, Ohio; ‡ Lyondell Chemical Company, Houston, Texas; and § Colorado State University, Fort Collins, Colorado

Received January 17, 2001; accepted July 17, 2001

A physiologically based pharmacokinetic (PBPK) model for isopropanol (IPA) and its major metabolite, acetone, is described. The structure of the parent chemical model, which can be used for either IPA or acetone by choosing the appropriate chemical-specific parameters, is similar to prevously published models of volatile organic chemicals such as styrene. However, in order to properly simulate data on the exhalation of IPA and acetone during inhalation exposures, it was necessary to expand the description of the lung compartment to include a subcompartment for the upper respiratory tract mucus layer. This elaboration is consistent with published PBPK models of other water-soluble vapors in which the mucus layer serves to absorb the chemical during inhalation and then release it during exhalation. In the case of IPA exposure, a similar PBPK structure is used to describe the kinetics of the acetone produced from the metabolism of IPA. The resulting model is able to provide a coherent description of IPA and acetone kinetics in the rat and human for exposures to IPA by several routes: intravenous, intraperitoneal, oral, inhalation, and dermal. It is also able to consistently reproduce kinetic data for exposures of rats or humans to acetone. Thus, the model provides a validated framework for performing chemical-specific route-to-route extrapolation and cross-species dosimetry, which can be used in place of generic default calculations in support of risk assessments for IPA and acetone.

Key Words: PBPK model; isopropanol; CAS# 67-63-0; acetone; CAS# 67-64-1.

Isopropanol (2-propanol, CAS# 67-63-0; IPA) is a volatile liquid that is miscible in both water and organic solvents. Due to its useful properties and low toxicity, IPA has been widely used for many years as a solvent, rubbing alcohol, and mild disinfectant. In spite, or perhaps because, of this long experience of human use, the toxicological data on IPA were, until recently, relatively limited. In response to the continued widespread use of IPA and the limited data available on its potential toxicity, the U.S. Environmental Protection Agency (U.S. EPA) promulgated a Final Test Rule in 1989 requiring that additional experimental testing be conducted to evaluate the pharmacokinetics and toxicity of IPA. The goal of the additional testing was to provide the experimental basis for a more confident evaluation of the potential human health risks from IPA exposure. Subsequent to this U.S. EPA action, a number of valuable studies of IPA toxicity and pharmacokinetics have been completed (Kapp et al., 1996). In particular, inhalation studies of IPA have demonstrated neurological effects (Burleigh-Flayer et al., 1994; Gill et al., 1995) and chronic renal toxicity (Burleigh-Flayer et al., 1997), and studies of IPA administration by the oral route have identified developmental and reproductive effects (Bevan et al., 1995; Tyl et al., 1994). The use of this newly available toxicity data in a state-of-the-art human health risk assessment presents several challenges. First, the studies of the reproductive and developmental endpoints have been performed by a different route of exposure than the studies of other potential noncancer effects, such as neurotoxicity. In the past, noncancer risk assessments have been performed on a route-specific basis, relying primarily on oral studies for an oral reference dose (RfD) and inhalation studies for an inhalation reference concentration (RfC). When necessary, conversion between oral doses and inhalation exposures was performed with rudimentary calculations of absorbed dose that did not take into consideration the physicochemical and pharmacokinetic properties of the chemical. More recently, however, the U.S. EPA has demonstrated an interest in the use of physiologically based pharmacokinetic (PBPK) modeling to perform direct comparisons of toxicity studies across routes of exposure (Fourman and Clewell, 1999; Gerrity and Henry, 1990). Indeed, in the recent U.S. EPA risk assessment for vinyl chloride (U.S. EPA, 2000), the inhalation RfC is based on the results of a study in which vinyl chloride was administered in the food (Til et al., 1991), using a PBPK model (Clewell et al., 1995) to perform route-to-route extrapolation.

The second challenge associated with the use of animal data for IPA in a human health risk assessment is uncertainty regarding the appropriate approach for performing cross-species dosimetry from the experimental animal to the human. The U.S. EPA RfC dosimetry guidelines (U.S. EPA, 1994) repre-
sent an important step forward in this regard, by providing multiple default approaches for cross-species dosimetry depending on the physicochemical properties of the compound and the nature of its toxicity. In these guidelines, inhaled vapors are classified into one of three categories: category 1 for reactive or readily metabolized gases and vapors for which accumulation in the systemic blood is unlikely (e.g., formaldehyde); category 2 for chemicals with intermediate properties; and category 3 for unreactive, poorly water-soluble chemicals that rapidly achieve a steady-state blood concentration (e.g., styrene). As an unreactive but highly water-soluble chemical, IPA cannot readily be classified into either category 1 or 3. Unfortunately, default dosimetry for category 2 chemicals is currently under development. However, even if such a default was available, the U.S. EPA guidelines indicate that the preferred methodology for cross-species extrapolation is the use of a validated PBPK model.

The purpose of the work described in this paper was to develop and validate a PBPK model for IPA and its principal metabolite, acetone, in the rat and human. The model was designed with the goal of providing a useful tool for integrating the existing toxicological data on IPA into a human health risk assessment. Specifically, the PBPK model is intended to perform route-to-route and cross-species dosimetry in support of the derivation of RfC and RfD values for IPA based on the results from toxicity studies in animals. Of course, the model could also be used in the same fashion to support a risk assessment for acetone exposure. This paper describes the development and validation of the basic PBPK model, with only one potential target tissue included (the brain, for acute neurological effects). Expansion of the model to support risk assessments for other potential target tissues will be the subject of a subsequent paper.

**MATERIALS AND METHODS**

**Model Structure**

The diagram for the PBPK model developed for the rat for IPA and its metabolite acetone is provided in Figure 1. The basic model structure is similar to previously published models of volatile organic chemicals, such as styrene (Ramsey and Andersen, 1984). The tissues represented in the model include those associated with uptake/excretion (lungs and skin) and metabolism (liver), with the remaining storage tissues separated into fat tissues, slowly perfused tissues (e.g., muscle), and rapidly perfused tissue compartments (other organs), according to their kinetic behavior (ratio of tissue blood flow to partition coefficient times volume). The brain was described separately from the other rapidly perfused tissues as an example of the treatment of a target tissue. Due to the high water solubility of IPA and acetone, we assumed that some absorption in the upper respiratory tract could occur during inhalation, with subsequent desorption during exhalation. This cyclic phenomenon had previously been reported for a number of water-soluble organic chemicals, including acetone (Gerde and Dahl, 1991; Johanson, 1986; Kumagai and Matsunaga, 1995; Kumagai et al., 1999). Initially, a simple fractional uptake approach, suggested by Johanson (1986), was used in the model. This simple approach was able to reproduce closed-chamber gas uptake data (Corley, unpublished data; Hallier et al., 1981) as well as blood concentration data from several of the inhalation data sets described below (Haggard et al., 1944; Slauter et al., 1994), using a fractional alveolar uptake of 0.7 for both IPA and acetone. However, the fractional uptake description was unable to reproduce exhaled air data from human IPA and acetone exposures (DiVincenzo et al., 1973; Kumagai et al., 1999; Wigaeus et al., 1981). To adequately reproduce this

![FIG. 1. PB-PK model for isopropanol and acetone. Abbreviations are defined in tables or, where used in equations, in the text.](https://academic.oup.com/toxsci/article-abstract/63/2/160/1713718)
Inhaled air data, it was necessary to add a description of the absorption and desorption of the chemicals in the upper respiratory tract during cyclic breathing, similar to the description used by Kumagai and Matsunaga (1995) in their model of acetone inhalation in the human. The following model code, which treats inhalation and exhalation as simultaneous, parallel processes, was developed for the lung compartment in order to incorporate the reservoir effect of the mucus layer of the upper respiratory tract on exhaled air concentrations (Fig. 1):

Amount in the mucus:

\[
\frac{d\text{Muc}_i}{dt} = \text{Cl}_{\text{MUC}} \cdot \left( \frac{\text{C}_{\text{INH}} - \text{C}_{\text{MUC}}}{\text{P}_{\text{MUC}}} \right)
\]

\[
\frac{d\text{Muc}_x}{dt} = \text{Cl}_{\text{MUC}} \cdot \left( \frac{\text{C}_{\text{MUC}} - \text{C}_{\text{ALV}}}{\text{P}_{\text{MUC}}} \right)
\]

Amount in the arterial blood:

\[
\frac{d\text{ArtBld}}{dt} = (\text{Q}_{\text{ALV}} \cdot \text{C}_{\text{ALV}}) - \frac{d\text{Muc}_i}{dt} - (\text{Q}_{\text{ALV}} \cdot \text{C}_{\text{ALV}}) + (\text{Q} \cdot (\text{C}_{\text{VEN}} - \text{C}_{\text{ART}}))
\]

Amount exhaled:

\[
\frac{d\text{Exh}}{dt} = (\text{Q}_{\text{ALV}} \cdot \text{C}_{\text{ALV}}) + \frac{d\text{Muc}_x}{dt}
\]

where Cl_{MUC} (l/h) represents the clearance of IPA or acetone in the upper respiratory tract, P_{MUC} is the partition coefficient between the respiratory mucus layer and the airstream, QC (l/h) is the total cardiac output, Q_{ALV} (l/h) is the alveolar ventilation rate, C_{VEN} and C_{ALV} (mg/L) are concentrations of IPA or acetone in the inhaled breath and alveolar region, respectively, and C_{MUC}, C_{VEN}, and C_{ART} (mg/L) are the concentrations in the mucus, venous blood, and arterial blood. In this description, Cl_{MUC} represents a clearance from the inhaled air into the mucus of the upper respiratory tract, as opposed to a fractional alveolar absorption (relative to alveolar ventilation) used in the simpler fractional uptake approach.

Model Parameters

Physiological parameters and partition coefficients were obtained from the available literature (Tables 1 and 2). Tissue volumes, blood flows, and resting ventilation rates were obtained from Brown et al. (1997). Ventilation rates and cardiac output during exercise in the human were taken from Astrand (1983). The tissue–blood and blood–air partition coefficients for IPA were taken from Kaneko et al. (1994). For acetone, the tissue–air partition coefficients in the rat were obtained from Fiserova-Bergerova and Diaz (1986), while the rat blood–air partition coefficient was taken from Morris and Cavanagh (1986). The human blood–air partition coefficient for acetone of 260 is an average value based on values reported in the literature ranging from 245 to 275 (Astrand, 1983; Morris and Cavanagh, 1986; Sato and Nakajima, 1979).

Metabolic and oral/IP absorption parameters were estimated by fitting of the model to informative data sets. A stepwise approach, described in detail below, was used for estimating the metabolic parameters, beginning with kinetic data from acetone exposures in the rat. Once the rat metabolic parameters for acetone were established, kinetic data from IPA exposures in the rat were used to estimate the metabolic parameters for IPA, holding the acetone metabolic parameters fixed. Data on controlled human exposures were then used to estimate the model parameter values in the human, using the rat values as a starting point. Where possible, kinetic data from different routes were used to validate the ability of the model to extrapolate kinetic behavior across routes using the same metabolic parameters. The model also is capable of generating a constant, exposure-independent background concentration of acetone in the blood and tissues representing endogenous production. The model parameters for the endogenous concentration (C_{ENDO}) and associated production rate (R_{ENDO}) shown in Table 1 are based on data reported by Kumagai et al. (1995), which indicated an endogenous acetone concentration of 0.5 mg/l in the adult male Japanese subjects studied.

Model Validation

Acetone pharmacokinetics in the rat. The closed chamber gas uptake data of Hallier et al. (1981) for four different starting concentrations of acetone were used to establish the metabolic parameters for acetone in the rat. Specifically, the V_{nas} and Km for acetone were estimated by fitting the model to the acetone chamber concentration data (Fig. 2a). A V_{nas} and Km of 7.5 mg/h/kg^{0.67} and 75 mg/L, respectively, were estimated from these data. These data were also used to estimate a clearance for acetone in the upper respiratory tract (Cl_{URS}) of 11 l/h/kg^{0.67}. (This scaled value is multiplied by the body weight

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Isopropanol/Acetone Rat and Human PBPK Model Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological parameters</td>
<td>Rat</td>
</tr>
<tr>
<td>BW Body weight (kg)</td>
<td>0.22</td>
</tr>
<tr>
<td>QC Cardiac output (l/h/kg^{0.67})</td>
<td>14.6</td>
</tr>
<tr>
<td>QP Pulmonary ventilation (l/h/kg^{0.67})</td>
<td>24.75</td>
</tr>
<tr>
<td>Blood flows (fraction of cardiac output)</td>
<td></td>
</tr>
<tr>
<td>QBm Brain</td>
<td>0.02</td>
</tr>
<tr>
<td>QFat Fat</td>
<td>0.07</td>
</tr>
<tr>
<td>QLiv Liver</td>
<td>0.183</td>
</tr>
<tr>
<td>QSkin Skin</td>
<td>0.058</td>
</tr>
<tr>
<td>QRap Rapidly perfused</td>
<td>0.557</td>
</tr>
<tr>
<td>QSlow Slowly perfused</td>
<td>0.17</td>
</tr>
<tr>
<td>Tissue volumes (fraction of body weight)</td>
<td></td>
</tr>
<tr>
<td>VAlv Alveolar blood</td>
<td>0.007</td>
</tr>
<tr>
<td>VBm Brain</td>
<td>0.006</td>
</tr>
<tr>
<td>VFat Fat</td>
<td>0.10</td>
</tr>
<tr>
<td>VLiv Liver</td>
<td>0.034</td>
</tr>
<tr>
<td>VMuc URT mucus layer</td>
<td>0.0001</td>
</tr>
<tr>
<td>VRap Rapidly perfused</td>
<td>0.044</td>
</tr>
<tr>
<td>VSlow Slowly perfused</td>
<td>0.65</td>
</tr>
<tr>
<td>Ds Dead space (fraction of lung volume)</td>
<td>0.15/0.25</td>
</tr>
<tr>
<td>Depth Skin depth (cm)</td>
<td>0.1</td>
</tr>
<tr>
<td>Uptake and clearance parameters</td>
<td></td>
</tr>
<tr>
<td>KAS Absorption from stomach/peritoneum (per/h)</td>
<td>2.0</td>
</tr>
<tr>
<td>KTSD Transfer from stomach to duodenum (per/h)</td>
<td>3.0</td>
</tr>
<tr>
<td>KAD Absorption from duodenum (per/h)</td>
<td>0.5</td>
</tr>
<tr>
<td>KTD Fecal excretion (per/h)</td>
<td>0.25</td>
</tr>
<tr>
<td>Cle Urinary clearance (l/h)</td>
<td>—</td>
</tr>
<tr>
<td>Cle Absorption into upper respiratory tract mucus (l/h/kg^{0.67})</td>
<td>11.0</td>
</tr>
</tbody>
</table>

* Study specific.
* Resting value. Higher values used during activity (Astrand, 1983).
* Subtracted from blood flow to slowly perfused tissue.
* Isopropanol/acetone.
* Dose-dependent: 5/h at low doses (<200 mg/kg), 0 at high doses (>1000 mg/kg), 2/h at intermediate doses.
estimated value for $Cl_{MUC}$ of 11 l/h/kg $^{3/4}$ provides a reasonable simulation of exposure from about 30 min to 5 h. As shown in Figure 2d, use of the previously estimated parameter $Cl_{MUC}$ for rats were conducted over a range of concentrations from 2110 to 126,600 ppm, providing support for the route-to-route extrapolation capability of the model. However, the data shown in Figure 2c suggests that the model predicts a more rapid approach to steady state than suggested by the data, but the simulated steady-state venous blood concentration is only 2c). The model predicts a more rapid approach to steady state than suggested by the data, but the simulated steady-state venous blood concentration is only 2258 or 4305 ppm acetone continuously by inhalation for 9 –12 days (Fig. 3a). The model was also able to reproduce the intraperitoneal data from Abshagen and Rietbrock (1969), but with an absorption rate from the peritoneum of 2/h (data not shown). The model was also used to simulate a data set on the dermal absorption of IPA and acetone in rats following intraperitoneal injection of 306 mg/kg were used to estimate a $V_{max}$ and $Km$ for the metabolism of IPA of 150 mg/hour/kg $^{3/4}$ and 500 mg/l, respectively (Fig. 3a).

IPA pharmacokinetics in the rat. Data reported by Slauter et al. (1994) on venous blood concentrations of IPA and acetone in rats following a single intravenous injection of 306 mg/kg were used to validate these metabolic parameters and to demonstrate the route-to-route capabilities of the model for IPA. An accurate simulation of the intraperitoneal data from Nordmann et al. (1973) was obtained with a peritoneal absorption rate of 5 h$^{-1}$ by slightly reducing the $V_{max}$ for IPA from 150 to 125 mg/kg/h $^{3/4}$ (Fig. 3b). Using the $V_{max}$ and $Km$ estimated from the Slauter et al. (1994) data, the model was also able to reproduce the intraperitoneal data from Abshagen and Rietbrock (1969), but with an absorption rate from the peritoneum of 2/h (data not shown).

Inhalation data was also used to validate the metabolic parameters for IPA. Slauter et al. (1994) provided data for IPA kinetics in rats following inhalation exposure (Figs. 3c and 3d). In this study, groups of rats were exposed to 476 or 4960 ppm IPA for 6 h, and venous blood concentrations of both IPA and acetone were measured during exposure and for 6 h postexposure. The model provided a reasonable fit to these data without requiring any adjustment of the model parameters from those established by the intravenous data. The model was also used to simulate a data set on the dermal absorption of IPA. In the Boatman et al. (1995) study, 1056 mg IPA/kg body weight was applied to a skin area of 4.3 cm$^2$ in a sealed cell, and left in place for 4 h, at which time the unabsorbed IPA was removed. The venous blood time courses of IPA and acetone were measured during the 4-h exposure period, as well as 20 h postexposure. Simulation of these dermal absorption data for IPA in the rat with the PBPK model required a permeation coefficient of 0.0008 cm/h (Fig. 4a), which compares well with the value of 0.0014 cm/h obtained in vitro with human skin by Blank et al. (1967). Interestingly, a substantial increase of the $V_{max}$ for IPA to 400 mg/h/kg $^{3/4}$ was necessary to obtain the observed ratio of IPA and acetone concentrations. To determine whether this increase reflected presystemic metabolism of IPA in the skin during absorption, the model was modified to include metabolism in the skin with the same affinity and capacity per gram of tissue as the liver. The resulting model was able to reproduce the kinetics of the dermal exposure using the same metabolic kinetics.

### TABLE 2

<table>
<thead>
<tr>
<th>Partition coefficients</th>
<th>Isopropanol</th>
<th>Acetone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rat</strong></td>
<td><strong>Human</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td><strong>Human</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Partition coefficients</strong></td>
<td><strong>Isopropanol</strong></td>
<td><strong>Acetone</strong></td>
</tr>
<tr>
<td>PB Blood/air partition</td>
<td>1290.0</td>
<td>848.0</td>
</tr>
<tr>
<td>PBrn Brain/blood partition</td>
<td>0.88</td>
<td>1.33</td>
</tr>
<tr>
<td>PFat Fat/blood partition</td>
<td>0.21</td>
<td>0.32</td>
</tr>
<tr>
<td>PLiv Liver/blood partition</td>
<td>0.76</td>
<td>1.16</td>
</tr>
<tr>
<td>PLq Saline/air partition</td>
<td>1500.0</td>
<td>1500.0</td>
</tr>
<tr>
<td>PRap Rapidly perfused tissue/blood partition</td>
<td>0.79</td>
<td>1.25</td>
</tr>
<tr>
<td>PSw Slowly perfused tissue/blood partition</td>
<td>0.85</td>
<td>1.3</td>
</tr>
<tr>
<td>PMuc Mucus/air partition</td>
<td>1290.0</td>
<td>848.0</td>
</tr>
<tr>
<td>P Skin Permeability coefficient (cm/hour)$^a$</td>
<td>0.0008</td>
<td>—</td>
</tr>
</tbody>
</table>

$^a$ Used in the estimation of $PS_{kin}$

$^b$ When exposure is not via the dermal route, this value is set to zero.
constants as for the other exposure routes (liver $V_{\text{max}}$ and $K_{\text{m}}$ of 150 mg/h/kg$^{3/4}$ and 500 mg/l, respectively).

Data from Nordmann et al. (1973) and Slauter et al. (1994) were used to estimate oral absorption parameters for IPA in the rat, as well as to provide support for the rat metabolic parameters estimated for IPA. In these studies, rats received a single oral administration of IPA at doses of 6000 mg/kg (Nordmann et al., 1973), 3056, or 330 mg/kg (Slauter et al., 1994). As in the case of acetone, a shift in the value for the stomach absorption parameter was necessary, suggesting faster absorption of IPA at the low dose ($K_{\text{AS}} = 5/h$, Fig. 4b), and slower absorption at the higher oral doses ($K_{\text{AS}} = 0$, Fig. 4c).

Plaa et al. (1982) also conducted oral IPA studies at four different oral doses in rats (79, 196, 786, or 1964 mg IPA/kg). The model again was able to provide a reasonable simulation of the data only when oral absorption parameters were adjusted to decrease the rate of absorption with increasing IPA dose (data not shown).

During the development of the IPA model, initial results from a gas uptake study with rats conducted by Corley (unpublished data) were obtained and were used to further validate the model. The ability of the model to simulate these data (Fig. 4d) provides additional support for the metabolic parameters for IPA reported in Table 2, as well as for the use of a value of 11 l/h/kg$^{3/4}$ for $C_{\text{MUC}}$ for IPA, which had been assumed by analogy to acetone.

**Isopropanol pharmacokinetics in the human.** Two controlled studies in which subjects ingested IPA were available to determine the capability of the model to simulate kinetics of IPA and acetone in the human following oral exposure to IPA (Lacouture et al., 1989; Monaghan et al., 1995). In the Monaghan et al. (1995) study, three healthy male subjects ingested 0.6 ml/kg 70% IPA in 240 ml water over a 5-min period. Venous blood samples were collected at baseline and 0.16, 0.33, 0.66, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h postingestion. Significant adjustments to the rat metabolism parameters for both IPA and acetone were required to reproduce these human data. Specifically, much higher affinity metabolic

---

**FIG. 2.** Model simulations of acetone kinetic data in the rat including: (a) closed chamber data reported by Hallier et al., 1981; (b) blood concentrations following ingestion of doses of acetone reported by Plaa et al., 1982; (c) continuous inhalation data reported by Haggard, 1944; and (d) 45-minute to 5-hour inhalation results reported by Haggard, 1944.
clearance for IPA ($V_{\text{max}}$ and $K_m$ of 300 mg/h/kg$^{3/4}$ and 10.0 mg/l, respectively) was necessary to reproduce the observed IPA data in the human (Fig. 5a). In contrast, a much lower metabolic capacity for acetone ($V_{\text{max}}$ and $K_m$ of 3.5 mg/h/kg$^{3/4}$ and 10.0 mg/l, respectively) was required to provide a reasonable simulation of the observed acetone data. It was also necessary to modify the oral absorption parameters from those in the rat. As shown in Table 1, a single set of oral uptake parameter values provided the best simulation of the human data, independent of dose.

A similar study was conducted by Lacouture et al. (1989), in which three male subjects ingested 0.4 ml/kg 70% IPA in 210 ml apple juice over 10 min. Validation of the human IPA metabolism and oral uptake parameter values derived from the data of Monaghan et al. (1995) was provided by the simulation of these data without any alteration of model parameters (Fig. 5b).

The results from the IPA inhalation study reported by Kumagai et al. (1999) were used to demonstrate the route-to-route extrapolation capability of the human IPA model. In this study, respiratory uptake in humans was investigated in four healthy male volunteers who inhaled concentrations of 50, 100, or 200 ppm acetone or IPA at rest for 10 min. The subjects inhaled the vapors through a mouthpiece equipped with a valve to isolate exhaled air, and samples of exhaled air were collected 1 min prior to exposure, during the 10-min exposure, and for 5 min following exposure. Exhaled air concentrations were reported both for the average concentration over an exhalation as well as for the concentration at the end of an exhalation (which would better represent air from the alveolar region). Model simulations of these data are provided in Figures 5c and 5d. The clearance in the upper respiratory tract ($C_{\text{MUC}}$) of 11 l/h/kg$^{3/4}$ identified in the rat resulted in a good fit to the concentrations of IPA observed in mixed (average) exhaled air and end-exhaled (alveolar) air, but it was also necessary to use a value of 0.15 for the fraction of dead space in the lung, as opposed to the value of 0.3 that is typically used for lipophilic compounds (Ramsey et al., 1984). Because the model fit to this data was highly sensitive to this parameter, the value obtained from this study is used in the model for both the human and the rat.
Acetone pharmacokinetics in the human. Data from Kumagai et al. (1999) were also used to validate the ability of the model to simulate inhalation of acetone in the human. The model simulations of the mixed-exhaled air and end-exhaled air following inhalation of 100 ppm acetone are presented in Figure 5d. No adjustments to the metabolic parameters were required to fit the data. Further, use of a value for $C_{LMUC}$ of 11 l/h/kg$^{3/4}$ for acetone in the human provided simulations that were consistent with the observed data. A fractional lung dead space of 0.25, which was also necessary to reproduce these data, was used in the model for all simulations of acetone inhalation.

Data reported by DiVincenzo et al. (1973) and Wigaeus et al. (1981) were used to validate the human $V_{max}$ and $K_m$ values for acetone that were estimated from the oral IPA studies. In the DiVincenzo et al. (1973) study, nine male volunteers were exposed via inhalation to 100 ppm or 500 ppm acetone vapor for 2 h. Using the human $V_{max}$ and $K_m$ values that were estimated from the oral IPA studies, the model was able to reproduce the data from this study for the concentration of acetone in venous blood (Fig. 6a). The results shown in this figure were obtained using the default value of 11 l/h/kg$^{3/4}$ for $C_{LMUC}$. A better fit to the data (not shown) could be obtained by increasing $C_{LMUC}$ to 20 l/h/kg$^{3/4}$. Reasonable agreement was also obtained with data from a similar study by Wigaeus et al. (1981) for acetone concentrations in exhaled air and arterial blood (Figs. 6b and 6c). The default value of 11 l/h/kg$^{3/4}$ for $C_{LMUC}$ was again used in performing this comparison. This study also provided the only data available on urinary excretion of acetone. In order to make use of this data, urinary clearance, described as a first-order clearance of the blood, was added to the model and the parameter ($C_{LUR}$) was estimated by fitting the data from Wigaeus et al. (1981) on the urinary excretion of acetone, shown in Figure 6d. The urinary clearance estimated from this data does not represent a significant route of elimination for IPA.

RESULTS AND DISCUSSION

A satisfactory description of diverse data in both rats and humans for IPA and acetone kinetics was obtained with the
development of a linked PBPK model for these two chemicals. With the model it was possible to simulate IPA and acetone kinetics in rats following dosing by five different routes of exposure. In addition, the model was capable of simulating data in humans following inhalation exposure of acetone or IPA or oral administration of IPA. The data, which were described by the PBPK model, were collected in different laboratories over a 50-year period. The consistency of the model parameters in describing such a diverse data set increases confidence that the model parameters are good representations of the physiological processes governing IPA and acetone disposition in experimental animals and humans.

The kinetic data for oral administration of both IPA and acetone in the rat consistently requires a dose-dependent parameterization for oral uptake. As indicated in Table 1, although a single value can be used for three of the four oral absorption parameters across all of the studies and doses, the parameter describing uptake from the stomach must be varied inversely with dose. For low doses, on the order of a few hundred milligrams per kilogram or less, rapid uptake is observed, consistent with a rate constant for uptake from the stomach of 5/h. At high doses, above 1000 mg/kg, much slower uptake is observed that is most effectively modeled with a rate constant of zero for stomach uptake, resulting in the transfer of all of the chemical to the second (duodenal) compartment, where it is absorbed over a longer period. A value between these two extremes was most appropriate for intermediate doses. The cause of this dose-dependent absorption is
unknown, but may be associated with a pharmacological effect of high doses of IPA/acetone on gastric absorption or gastric emptying. The evidence for its occurrence is consistent across three different studies and for both IPA and acetone. The only impact of this dose dependency is for applying the PBPK model to predict kinetics following oral gavage, in which case the model parameter for gastric absorption must be set to a value ranging from 5/h to 0/h as determined by comparing the administered dose to the ranges shown in the footnote to Table 1.

The human kinetic data uniformly require a much higher affinity metabolic clearance for IPA in the human than that required by the kinetic data in the rodent. Unfortunately, there are no *in vitro* metabolic data available for IPA oxidation to support or refute the parameter values based on these *in vivo* data. It is possible that the apparently higher affinity of metabolism in the human reflects a contribution at low concentrations from another enzyme with a higher affinity than ADH. A low-capacity, mixed-function oxidase has been implicated in the oxidation of ethanol and trichloroethanol in the human (Muller et al., 1975).

**Lung Description**

Traditionally in PBPK modeling of organic solvents, uptake in the respiratory tract has been assumed to occur only in the alveolar region (Ramsey and Andersen, 1984). The results of experimental studies conducted by Astrand (1983) in humans...
indicated that uptake was much lower than expected in the case of water-soluble solvents, such as n-butanol. Astrand (1983) concluded that a water-soluble solvent can be absorbed into the mucus of the upper respiratory tract during inhalation and then desorbed during exhalation, resulting in less of these solvents reaching the alveolar region of the respiratory tract. Therefore, for water-soluble organic solvents such as acetone or IPA, the traditional description of the lung compartment does not consider the important role of the mucus layer of the upper respiratory tract in inhalation uptake.

For this model, a slightly more complex lung description was incorporated, similar to the description used by Kumagai and Matsunaga (1995) in their model of acetone inhalation in the human. It incorporates a dual compartment mucus description, with parallel subcompartments for inhalation and exhalation. A simpler fractional uptake description, as used by Johanson (1986) for modeling human inhalation of 2-butoxyethanol, provided an adequate simulation of venous blood concentrations during inhalation exposures. However, the more complex description was necessary in order to adequately describe data on concentrations of acetone and IPA in exhaled air (DiVincenzo et al., 1973; Kumagai et al., 1999; Wigaeus et al., 1981). With this more complex description it was possible to reproduce the role of upper respiratory tract mucus in the reversible absorption of these water-soluble compounds. It is of interest that in order to reproduce these inhalation data, it was also necessary to reduce the fractional dead space in the lung from the usual value of 0.3 for lipophilic compounds to values of 0.25 for acetone and 0.15 for IPA. The smaller apparent fractional dead space likely reflects the possibility that for highly water-soluble compounds like IPA and, to a lesser extent, acetone, uptake can extend beyond the alveolar region into the mucus-covered areas of the tracheobronchial region. On the other hand, the simpler description was useful in providing a direct estimate of the fractional uptake of IPA and acetone during inhalation. For both chemicals, the available inhalation data (Corley, unpublished data; Haggard et al., 1944; Hallier et al., 1981; Slauter et al., 1994) were consistent with a fractional uptake of approximately 70% of alveolar ventilation. That is, the fractional uptake of IPA and acetone was estimated to correspond to roughly 70% of that expected from the usual alveolar ventilation rates used in PBPK models of lipophilic vapors (Ramsey and Andersen, 1984).

Published estimates of fractional uptake are more typically measured relative to total ventilation; for comparison with these other data, the fractional uptake of IPA and acetone estimated in this analysis equates to approximately 50% of total ventilation (multiplying by 0.67, the ratio of alveolar to total ventilation). A similar fractional uptake of 60% based on total ventilation was estimated by Johanson (1986) for 2-butoxyethanol, and the data reported by Astrand et al. (1976) for n-butanol are consistent with an initial pulmonary extraction of roughly 60%. Unfortunately, many estimates of fractional uptake reported in the literature have been obtained at or near steady state and are therefore highly dependent on metabolic extraction. Fractional uptakes at steady state estimated from these data are not comparable to initial fractional uptakes, which must be derived by the extrapolation of uptake data to estimate the initial extraction when the blood concentration is negligible (Astrand et al., 1976).

It was mentioned earlier that the inclusion of metabolism in the skin was necessary to reproduce data from dermal exposure to IPA. During the development of this model, we also investigated the potential impact of metabolism of IPA in the lung by including it in the model in a similar fashion to the description of metabolism in the skin. Our results indicated that the impact of lung metabolism was too small to be of consequence for the prediction of systemic exposure concentrations. In particular, the available kinetic data (particularly exhaled air data) was not consistent with a level of presystemic lung metabolism sufficiently high to alter systemic delivery. Of course, if the lung were a target tissue for toxicity, the metabolism in the Clara cell–rich region would have to be described to determine its impact on local dosimetry.

Model Application

The PBPK model presented here is intended to perform route-to-route extrapolation and cross-species dosimetry in support of an IPA or acetone risk assessment. The ultimate aim of using PBPK modeling in risk assessment is to provide a suitable measure of internal exposure, referred to as the PBPK dose metric, which better represents the biologically effective dose, that is, the dose that causally relates to the toxic outcome. The PBPK dose metric can then be used in place of default dose metrics (e.g., inhalation exposure concentration or administered dose) during risk assessment calculations (Andersen et al., 1987; Clewell and Andersen, 1985; Jarabek, 1995; Young et al., 1996).

In the past, risk assessments for different routes of exposure have generally been performed separately, with the quantitative dose-response calculations in each case being based solely on studies performed by the route of interest for that assessment. A drawback of this approach is that it is not possible to address concerns regarding effects observed in a study by a different route that might represent a more sensitive end point than the critical study by the route of interest. Occasionally, comparisons of inhalation and oral studies have been performed by calculating an inhaled dose, defined as the product of the inhalation concentration, the pulmonary ventilation rate, the duration of exposure, and an estimate of the fractional uptake. However, as discussed earlier, the fractional uptake for a volatile chemical can have a complex time dependence. Moreover, inhaled dose may not provide a meaningful measure of internal exposure. A more correct approach for comparing studies across routes is the use of a PBPK model. Specifically, pharmacokinetically equivalent exposures across routes (and
species) can be defined as those producing the same value of the appropriate PBPK dose metric.

To illustrate the use of the PBPK model reported here to support the comparison of toxicity data across exposure routes, Figure 7 presents the model-predicted dose response for the maximum concentration ($C_{\text{MAX}}$) and area under the concentration curve (AUC) for isopropanol and acetone following a single oral dose (a, b) or inhalation exposure for 6 h (c, d) in the rat. The parameter values for the rat in Tables 1 and 2 were used for this comparison. As a simple example of the interpretation of Figure 7, if the dose for a particular oral study in rats was 800 mg/kg and the AUC for IPA was assumed to be the appropriate measure of exposure for the end point observed in the study, Figures 7a and 7c could be used to estimate the equivalent 6-h inhalation exposure concentration. First, from Figure 7a it can be determined that the model-predicted value of the dose metric (AUC for IPA) for an oral dose of 800 mg/kg IPA is approximately 2300 mg-h/l. Then, from Figure 7c, it can be determined that an AUC for IPA of 2300 is predicted to occur for a 6-h exposure to IPA at a concentration of roughly 2800 ppm. Thus, if the AUC for IPA is the appropriate basis for comparison, 6-h inhalation exposure of the rat at a concentration of 2800 ppm IPA would be predicted to result in the same potential for systemic toxicity as oral dosing with 800 mg/kg IPA.

Similarly, the PBPK model could be run with the parameter values for the human from Tables 1 and 2 to determine the continuous (24 h/day) IPA inhalation exposure concentration that would produce a daily AUC for IPA of 2300 mg-h/l in the human. The inhalation concentration obtained in this fashion would represent the human equivalent concentration (HEC) for the oral dose of 800 mg/kg in the rat, on the assumption that the
AUC for IPA is the appropriate measure of internal exposure. As can be seen from Figure 7, however, maximum concentrations of acetone achieved in the blood of the rat after exposure to IPA are predicted to be in the same range as those of IPA itself. Therefore, for effects observed following IPA exposure, selection of the appropriate pharmacokinetic dose metric should consider whether the effect is produced by IPA itself, by its metabolite, acetone, or by the coexposure to the two compounds.

In an actual risk assessment, the model would be run to reproduce the specific exposure scenario in each of the studies demonstrating effects from IPA or acetone. PBPK dose metrics derived for these various studies would make it possible to determine the critical effects (those occurring at the lowest human exposure levels), based on all of the available animal studies, regardless of the route of exposure used in the different studies. Use of the appropriate PBPK dose metric for the critical effect in the animal-to-human extrapolation, in place of the application of default dosimetry, would then provide a more biologically realistic basis for evaluating the potential risks associated with human exposures to IPA or acetone.

ACKNOWLEDGMENTS

This model development was supported by the Isopropanol and Acetone Panels of the American Chemistry Council.

REFERENCES


Morris, J. B., and Cavanagh, D. G. (1986). Deposition of ethanol and acetone

Downloaded from https://academic.oup.com/toxsci/article-abstract/63/2/160/1713718 by guest on 22 March 2019


