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Derivation of occupational exposure limits based on target blood concentrations in humans

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Abstract

An approach for deriving occupational exposure limits (OEL) for pharmaceutical compounds is the application of safety factors to the most appropriate pre-clinical toxicity endpoint or the lowest therapeutic dose (LTD) in humans. Use of this methodology can be limited when there are inadequate pre-clinical toxicity data or lack of a well-defined therapeutic dose, and does not include pharmacokinetic considerations. Although some methods have been developed that incorporate pharmacokinetics, these methods do not take into consideration variability in response. The purpose of this study was to investigate how application of compartmental pharmacokinetic modeling could be used to assist in the derivation of OELs based on target blood concentrations in humans. Quinidine was used as the sample compound for the development of this methodology though the intent was not to set an OEL for quinidine but rather to develop an alternative approach for the determination of OELs. The parameters for the model include body weight, breathing rate, and chemical-specific pharmacokinetic constants in humans, data typically available for pharmaceutical agents prior to large scale manufacturing. The model is used to simulate exposure concentrations that would result in levels below those that may result in any undesirable pharmacological effect, taking into account the variability in parameters through incorporation of Monte Carlo sampling. Application of this methodology may decrease some uncertainty that is inherent in default approaches by eliminating the use of safety factors and extrapolation from animals to humans. This methodology provides a biologically based approach by taking into consideration the pharmacokinetics in humans and reported therapeutic or toxic blood concentrations to guide in the selection of the internal dose-metric.

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1. Introduction

An approach for deriving occupational exposure limits (OEL) for pharmaceutical compounds is the application of uncertainty or safety factors to the most appropriate pre-clinical toxicity endpoint or the lowest therapeutic dose (LTD) in humans (Agius, 1989; Galer et al., 1992; Sargent and Kirk, 1988). The safety factors are assumed to account for the prevalence of response [No Observable Adverse Effect Level (NOAEL) or Lowest Observable Adverse Effect Level (LOAEL)], inter-species extrapolation (animal to human), variability

in response (intra-subject), length of study (acute, sub-chronic, and chronic), and significance of response (reversible or irreversible). Individual safety factors range from 1 to 10 while the composite factor ranges from 1 to 1000 (Galer et al., 1992).

The application of default uncertainty or safety factors to the most appropriate pre-clinical endpoint or LTD can be limited when there are inadequate pre-clinical toxicity data or lack of a well-defined therapeutic dose. This would be inclusive of, though not limited to, drugs developed and used in humans prior to the enactment of the Federal Food, Drug, and Cosmetic Act (FDAC) in 1938 or those that require dose selection on the basis of therapeutic blood concentrations. While the basis for the assumption regarding the safety of drugs used prior to the FDAC may be practical for therapeutic

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exposure, this assumption does not extrapolate to occupational exposures over the period of a working lifetime. Pharmaceutical agents are designed to alter physiological or biochemical processes in a patient, which is undesirable for healthy workers. Additionally, the lack of a well-defined therapeutic dose likely occurs with agents that have a narrow therapeutic index or when inter-individual differences in pharmacokinetics can increase or decrease the blood concentration enough to alter the desired pharmacological response.

A considerable amount of effort has been placed on the reduction of uncertainty inherent in the application of default safety factors when deriving OELs (Dourson et al., 1996; Renwick and Lazarus, 1998). For example, the safety factors for variability in response and interspecies extrapolation, typically 10 each, have been modified to account for the relative contribution of toxicokinetic and toxicodynamic differences (Renwick, 2000; Renwick and Lazarus, 1998; World Health Organization, 1994). In the case of interspecies extrapolation, the safety factor is a composite of 4.0 and 2.5 for toxicokinetic and toxicodynamic differences, respectively (World Health Organization, 1994). In the case of intra-species variability, the safety factor is a composite of 3.2 each for toxicokinetic and toxicodynamic differences (World Health Organization, 1994). Each of these respective components can be revised when appropriate information is available to provide data derived safety factors.

Other methods have been developed to include pharmacokinetic considerations in the determination of OELs. For example, Sargent and Kirk (1998) simulated an 8 h per day, 5 days per week inhalation exposure to amitryptiline using a two-compartment model that assumed first order absorption and elimination. The maximum plasma level at 75 mg, the therapeutic dose, was 1 ng/mL which is equivalent to a total body burden of 1.5 mg/kg. The author's suggestion was to either apply a steady-state factor or control of overexposure (i.e., limit hours of exposure) since the NOEL was lower (1 mg/kg).

Methods have also been developed to adjust OELs for short term exposures or unusual work shifts and typically rely on the application of half-life to estimate risk, the assumption being that the drug will be completely eliminated by the next exposure day if the half-life is less than 3 h (Hickey and Reist, 1977; Verma, 2000). Reduction factors are also applied to the OEL for exposures less than 8 h per day, 5 days per week (Brief and Scala, 1975; Hickey and Reist, 1977, 1979; Sargent and Kirk, 1998). However, the initial OEL to which the reduction factor is applied is determined using the default approaches described above and thus has limitations.

Although methods have been developed to incorporate pharmacokinetics, they do not take into account

variability in parameters or responses. Mean values for pharmacokinetic parameters are used in calculating the safe exposure limit. Additionally, the volume of air used to determine exposure from the inhalation route is constant (10 m³/8 h shift) and is based on the assumption that a male engaging in light work has a tidal volume of 1000 cm³ and a breathing rate of 20 breaths/min during an 8 h shift (Galer et al., 1992).

The most extensive and biologically relevant incorporation of pharmacokinetics to determine safe exposure levels is the application of physiologically based pharmacokinetic (PBPK) modeling (Sweeney et al., 2001; Thomas et al., 1996). PBPK models are especially useful for determining safe exposure levels when human data are unavailable because they are designed in such a way as to facilitate interspecies extrapolation through the inclusion of anatomical, biological, and chemical-specific parameters, all of which have the potential to influence exposure. Variability in anatomical, biological processes, and pharmacokinetic parameters is also provided by incorporating Monte Carlo sampling into PBPK models (Thomas et al., 1996). More recently, PBPK models have been linked to pharmacodynamic models to predict not only exposure, but response at a given exposure level. As such, these models decrease uncertainty inherent in default approaches to human health risk assessment.

The application of PBPK models in the derivation of OELs has been primarily applied to environmental chemicals rather than pharmaceutical agents. This is in part due to the availability of pharmacokinetic and pharmacodynamic data from animals and humans exposed to pharmaceutical agents, which may obviate the need for interspecies extrapolation and use of a PBPK model which can be data intensive.

The purpose of this study was to investigate how application of compartmental pharmacokinetic modeling could be used to assist in the derivation of OELs using target blood concentrations in humans to guide in the selection of the internal dose-metric. Use of this type of modeling to determine OELs is appealing because the data required for the development of the model are collected as part of the drug development process. Additionally, variability in the physiological, anatomical, and pharmacokinetic parameters can be incorporated by use of Monte Carlo sampling. The model can be used to predict a threshold dose below which no subjects have blood concentrations reported to produce pharmacological effects in humans. Although the selection of the threshold dose is subjective, at least in part, the advantages of this approach are its use of human pharmacokinetic data, consideration of the variability in model parameters, and use of internal dose-metrics (i.e., the therapeutic blood concentration), each of which reduce uncertainty in deriving OELs.

2. Methods

2.1. Selection of test compound

The current approach may be used to derive an OEL for any pharmaceutical compound with known therapeutic or toxic blood levels and whose pharmacokinetics can be described using compartmental modeling. Quinidine, an antiarrhythmic agent, was chosen as a sample compound for the development of this methodology because the pharmacokinetics and therapeutic blood concentrations of quinidine have been well characterized in humans (Winters, 1994). Additionally, information typically available for the derivation of OEL's, such as a NOAEL derived from pre-clinical toxicity data or a low therapeutic dose in humans, are not available or not clearly defined. Daily doses used to treat arrhythmia are adjusted based on the cardiovascular state of the patient to obtain therapeutic blood concentrations of 2–6 mg/L whereas toxicity is seen at 8 mg/L (Verme et al., 1992). Typical toxic responses include diarrhea, nausea, vomiting, and esophagitis but can also include exacerbation of the cardiac effects and cinchonism (Roden, 1996). The pre-clinical toxicity data for quinidine are limited because it has been used as an antiarrhythmic agent since the 1920s, a time preceding the requirement for intensive pre-clinical toxicity or safety studies (reviewed by Roden, 1996).

2.2. Basic model structure

A one-compartment pharmacokinetic model was developed using the software ACSL (Advanced Continuous Simulation Language, Aegis, Huntsville, AL). Two- or three-compartment models can be used for other compounds if dictated by the blood concentration-time profiles. Although the pharmacokinetics of quinidine can be described using a two compartment model, the distribution phase is so rapid that a one compartment model is adequate (Winters, 1994).

A schematic diagram is outlined in Fig. 1. RA_{INH} is the rate of input from an inhalation exposure (mg/h), the typical route of occupational exposure and K_{EL} (h^{-1}) is

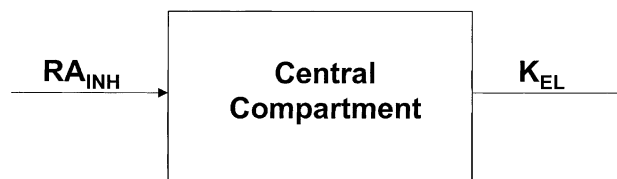


Fig. 1. Schematic diagram of the pharmacokinetic model for quinidine.

the first order elimination rate constant. RA_{INH} is described by the following equation:

$$RA_{INH} = \text{Conc} \times [\text{QPC} \times \text{BW}], \quad (1)$$

where Conc is the exposure concentration (mg/L air), QPC is the breathing rate (L/h/kg), and BW is the body weight (kg).

The equation used to describe the rate of change in the concentration of the drug in the central compartment, RAC (mg/h), is:

$$RAC = RA_{INH} - (K_{EL} \times A). \quad (2)$$

Integration of Eq. (2) provides the amount of drug in the central compartment (A; mg). The concentration of drug in the central compartment (CV; mg/L) is described by:

$$CV = A/VD_{APP}, \quad (3)$$

where VD_{APP} is the apparent volume of distribution (L/kg BW). The assumptions of the model were that 100% of the inhaled compound was bioavailable and that the concentration of the drug in the central compartment is representative of the blood and tissues that receive significant blood flow. The quinidine pharmacokinetic parameters used in the model are outlined in Table 1.

2.3. Incorporation of Monte Carlo simulation

Monte Carlo simulations were used to generate the distribution of input parameters (K_{EL} , VD_{APP} , QPC, and BW) using ACSLMath. Sets of input parameters (1000 Monte Carlo iterations) were generated for each simulated exposure concentration (see below "Application of the Model"). The means and standard deviations used to generate the distribution of parameters are

Table 1
Parameters used in the quinidine pharmacokinetic model

Parameter	Variable name	Mean	SD	Sample distribution
Body weight ^a	BW	70	9	Log normal
Breathing rate ^b	QPC	7.86	1.62	Log normal
Elimination rate ^{c,d}	K_{EL}	0.1118	0.0324	Normal
Volume of distribution ^{c,e}	VD_{APP}	2.7	1.2	Normal

^a kg; Thomas et al. (1996).

^b L/h/kg BW; Adams (1993).

^c Verme et al. (1992).

^d h^{-1} .

^e L/kg BW.

presented in Table 1. It was assumed that the pharmacokinetic parameters for quinidine (K_{EL} and VD_{APP}) were normally distributed and that ventilation rate and body weight were log normally distributed. The distribution of chemical-specific parameters may change depending on the compound but the ventilation rate and body weight are always log normally distributed.

Simulations were truncated to three standard deviations with the exception of the lower bound for volume of distribution, which was truncated to total blood volume (5222 mL/kg BW; Mann et al., 1996).

2.4. Sensitivity analysis

Sensitivity analysis was performed by increasing individual parameter values by 5% and noting the change in peak blood concentration. The simulated dose was 100 mg/m^3 and the parameters not being assessed were set at the mean values presented in Table 1. Peak blood concentration was most sensitive to changes in changes in K_{EL} . A 5% change in K_{EL} resulted in a 2.8% change in peak blood concentrations. An increase of 5% in the ventilation rate (QPC) and volume of distribution (VD_{APP}) resulted in proportional changes in peak blood concentrations (5%).

3. Application of the model

The model was used to predict target peak quinidine blood concentrations at steady state with exposure for 8 h per day, 5 days per week. In order to determine the length of the simulation necessary to insure that steady-state levels were achieved, simulations were carried out using the lower bound K_{EL} value (3 SD), 0.209 h^{-1} , and the mean parameters outlined in Table 1. At these values, steady-state blood concentrations were achieved within 240 h (Fig. 2).

Simulations were subsequently performed at exposure concentrations ranging from 1 to 400 mg/m^3 using the distribution of input parameters generated from the Monte Carlo simulations. A different set of input parameters (i.e., a different set of 1000 subjects) was used for each simulated exposure concentration. The percentage of subjects with peak steady-state quinidine blood concentrations greater than or equal to a target level, defined as percent responders, was determined at each exposure concentration. In order to be inclusive of concentrations that produce any undesirable physiological alterations, the target blood level selected ranged from 0.10 to 3.0 mg/L (Verme et al., 1992; Winters, 1994). A logistic fit of the simulated percent responders versus exposure concentration provided an estimate of the threshold dose below which no subjects (out of 1000) were predicted to have peak blood concentrations greater than or equal to the target blood level selected (Fig. 3).

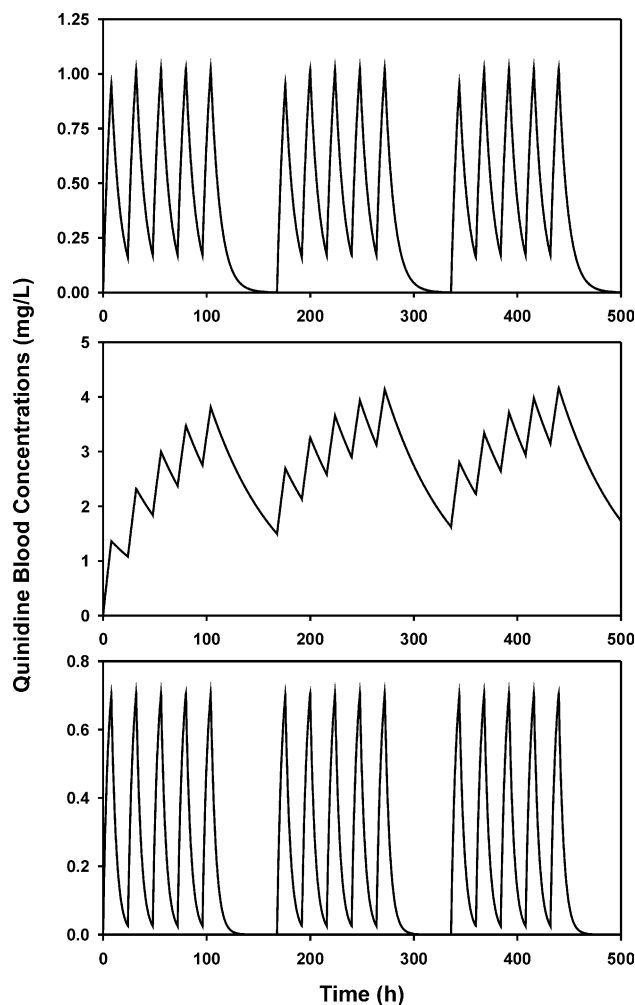


Fig. 2. Simulated quinidine blood concentrations with exposure to 100 mg/m^3 for 8 h per day, 5 days per week. Simulations were obtained using a K_{EL} value of 0.0146 h^{-1} (top panel), 0.1118 h^{-1} (middle panel) and 0.2090 h^{-1} (bottom panel), and the mean values for all other parameters outlined in Table 1.

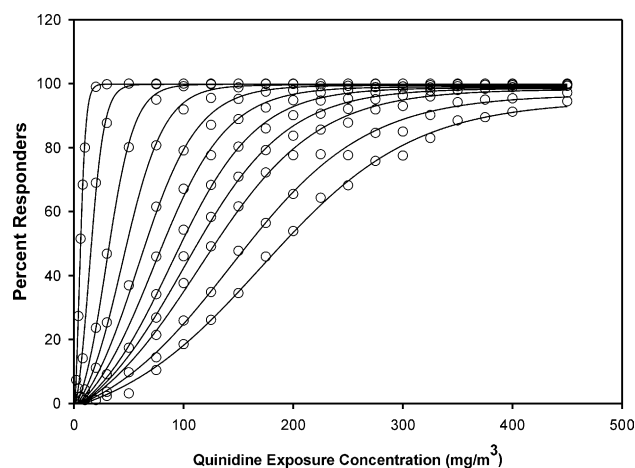


Fig. 3. Logistic fit of percent responders versus quinidine exposure levels. A responder was defined as a simulated subject with a peak blood quinidine concentration equal to or greater than the target blood level selected.

Linear regression analysis of the threshold concentration versus target blood level (Fig. 4) provided the following linear equation to be used to determine the exposure concentration for a given risk level:

$$Y = 2.9169(X) + 1.5506, \quad (4)$$

where X is the peak quinidine blood concentration (target blood level; mg/L) and Y is the quinidine exposure threshold (OEL; mg/m³). Once the target blood level is selected the equation can be solved to provide the exposure concentration at which no subjects are predicted to have peak blood concentrations greater than or equal to the target blood level selected. For example, using Eq. (4), the exposure concentration below which no subjects are predicted to have peak blood levels greater than or equal to 2 mg/L, the lowest therapeutic blood concentration, is ~ 7 mg/m³.

The application of this type of model is not specific to quinidine as the same approach can be used for other compounds. The structure of the model may differ (i.e., one-, two-, or three-compartments) but the logistic regression of the simulated percent responders versus exposure concentration would still be obtained for the specific compound. The regression would then be used to provide an estimate of the threshold dose below no subjects will have peak blood concentrations equal to or greater than the selected target level which causes any undesirable pharmacological effect for a particular compound. The overall approach described above can also be applied to area under the blood concentration-time curve (AUC). Use of AUC rather than peak blood concentrations may be more appropriate for instances where toxicity is related to total body burden over the course of exposure. Similarly, this approach may also be applied to mean concentrations.

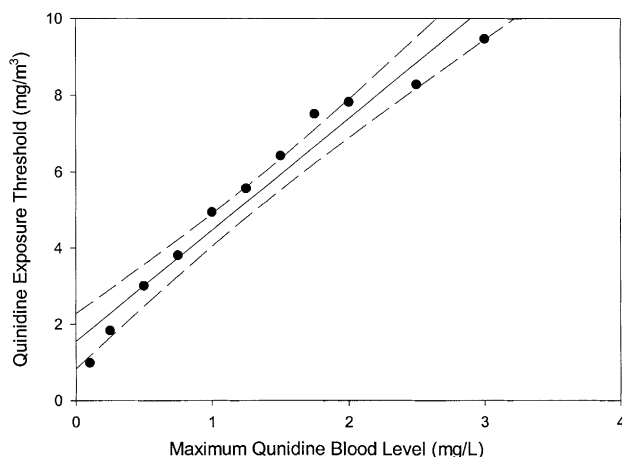


Fig. 4. Target quinidine exposure threshold concentration versus target blood level selected. The symbols represent the simulated threshold exposure concentration that was obtained from the logistic fit of the data illustrated in Fig. 3. The solid line is the linear regression analysis with the 95% confidence intervals (dotted lines).

4. Discussion

The methodology typically used for deriving OELs for pharmaceutical compounds is the application of safety or uncertainty factors to the most relevant pre-clinical toxicity endpoint or the LTD in humans. In recent years, much emphasis has been placed on the validity of the use of default safety or uncertainty factors (Dourson et al., 1996; Renwick and Lazarus, 1998). At issue are the biological relevance and whether OELs derived using the standard methodology provide enough protection for susceptible populations or whether they are overly conservative and place undue burden on manufacturers. Additionally, the NOAEL value is highly dependent on the study design and may not accurately determine the dose at which adverse effects may be seen even in animals. It may also be based on effects observed in animals that are not relevant to humans. In the pre-clinical safety assessment of pharmaceutical compounds, the choice of animal species should be based on similar metabolic profiles between animals and humans. However, the most sensitive toxicity endpoint is still used for determination of OELs irrespective of these criteria.

In an effort to address these concerns, the safety factors that account for inter-species extrapolation and intra-species variability have been modified to provide data derived safety factors that are based on appropriate knowledge of the toxicokinetics or toxicodynamics of the compound of interest (World Health Organization, 1994). Methods have also been derived to account for pharmacokinetics in deriving OELs, for either standard or short term exposure limits (Verma, 2000).

Although these approaches are more biologically based than default approaches, there are several issues that limit their application, most importantly the exclusion of variability concepts. While there is a safety factor that accounts for inter-individual variability, the formula for determination of the OEL for pharmaceutical compounds is still applied to a single NOAEL from animal studies or the LTD in humans. When the pharmacokinetic factors are taken into account, the reliance is on mean pharmacokinetic parameters, and default safety factors are still applied.

The methodology presented above includes pharmacokinetics and variability in parameters that can alter exposure by incorporating Monte Carlo sampling into compartmental pharmacokinetic modeling. Using this approach to simulate safe exposure levels for pharmaceutical compounds is particularly appealing because it is not as data intensive as a PBPK model and relies on data normally collected as part of the drug development process (i.e., pharmacokinetics and therapeutic or toxic blood concentrations in humans). Factors that may alter exposure and hence the toxicity (i.e., susceptibility) can be accounted for by simulating the distribution of model

Table 2
Comparison of occupational exposure limits for quinidine

Study	Endpoint	Value	Safety factor	OEL
10-week rat ^a	Cardiac EEG changes	25 mg/kg/day	324	0.54 mg/m ^{3b}
Clinical dose	Antiarrhythmia	600 mg/day	300	0.20 mg/m ^{3b}
PK Model	Peak blood level	2.0 mg/L	None	7.38 mg/m ^{3c}

^a Zbinden and Spichiger (1982).

^b Calculated using the method described by Sargent and Kirk (1988) and assuming a breathing rate of 10 m³/8-h work shift and 70 kg BW.

^c Calculated using Eq. (4).

parameters expected to be seen in the general population. For example, the pharmacological and toxicological effects of quinidine are known to be affected by the cardiac state or by hepatic impairment that is secondary to alteration of the VD_{APP} and clearance. The VD_{APP} of quinidine ranges from 1.8 to 3.8 L/kg BW, depending on the health status (Winters, 1994). These values are within the range generated by the Monte Carlo sampling method thus illustrating the importance of the inclusion of variability and the ease at which this can be incorporated into the risk assessment.

Moreover, if the bioavailability is less than complete with inhalation exposure the CONC term (Eq. (1)) can be modified to account for the extent of absorption by inhalation exposure (i.e., $CONC \times \text{Fraction absorbed}$). Less than complete bioavailability with oral administration is already factored into the analysis by using the blood concentrations as the internal dose metric. The oral bioavailability of quinidine can range from 47% to 96%, while the therapeutic blood concentration has a more narrow range of 2–6 mg/L (Winters, 1994). Factors which may alter the bioavailability, such as first pass clearance, are already accounted for in the pharmacokinetic model with Monte Carlo simulations.

Although this methodology provides a more biologically based approach for determination of OELs, the subjective nature of the derivation of OELs is not entirely eliminated. The selection of the target blood level upon which to base the OEL still relies on scientific judgement. However, the OEL is based upon the choice of a target blood level as opposed to external dose-metric, and accounts for variability in parameters which may influence exposure and hence toxicity.

Table 2 provides a comparison of OELs for quinidine derived using the current methodology and standard approaches. The safety factors for derivation of the OEL based on the pre-clinical toxicity endpoint, cardiac EEG changes noted in a rat toxicity study (Zbinden and Spichiger, 1982), accounted for prevalence of response (NOAEL), species differences (rat), study length (10 weeks), lack of a uniform dose–response curve, and significance of effects (reversible but serious). The OEL derived from the LTD, 0.20 mg/m³, was determined assuming that a significant response is prevalent at the low end of the therapeutic dose, that there is a steep dose–response curve (i.e., narrow therapeutic index), and that

the effects are serious but reversible. The assumptions in each case were that 100% of the inhaled compound is absorbed, and that 10 m³ of air are inhaled during an 8-h shift by a health 70 kg worker.

It should be noted that the data in Table 2 are provided for the purpose of comparisons between different methodologies and is not for the purpose of advocating a specific OEL for quinidine. Nevertheless, it is interesting to note that the most conservative OEL was based on the therapeutic dose in humans, while the least conservative was based on the pharmacokinetic model predictions. This is likely due, at least in part, to the fact that blood concentrations are more directly related to toxicity than dose, and hepatic clearance or first pass metabolism is not considered at all in the standard approach. Although the current methodology proposed conservatively assumes that 100% of the inhaled compound is bioavailable, the reliance is still on blood concentrations as the dose-metric, a more accurate predictor of toxicity than administered dose. Safety or uncertainty factors are not required for this approach which may also account for the differences.

In summary, the methodology presented may provide a more reliable alternative for determining OELs than default approaches particularly when clinical pharmacokinetic data are available. It also provides a more biologically based approach by taking into consideration factors which may influence internal exposure and response, such as physiological and anatomical parameters (i.e., body weight and ventilation rate), and pharmacokinetic constants (i.e., volume of distribution and elimination rate). Uncertainty is decreased by incorporating variability in parameters which may alter exposure.

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