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COMPARISON OF THREE PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODELS OF BENZENE DISPOSITION

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ABSTRACT

We assess the goodness of fit of three physiologically-based models of benzene pharmacokinetics to experimental data in Fischer-344 rats. These models were independently developed and published. Large differences in the quality of the fit are observed. In addition, the parameter values leading to acceptable fits are spread over the entire range of physiologically plausible values and can be quite different from average or standard values. On the other hand, choosing standard values for the parameters does not ensure good predictions of all tissue levels. These results emphasize the difficulty of a rigorous calibration of physiological models, and the need for further research in this area. For risk assessment purposes, simpler models, making equivalent use of the crucial data, are probably preferable.

INTRODUCTION

Three physiologically based pharmacokinetic (PBPK) models describing the distribution of benzene in mammals have recently been proposed (Medinsky et al., 1989b; 1989c; Travis et al., 1990; Woodruff et al., 1989). These models have similar structures, as expected for physiological models, but differ in their parameter values for the same species. Both the way in which the parameters were derived, and differences in the experimental data used to fit them, explain the discrepancies. In the work of Medinsky et al. (1989b; 1989c) the model was adjusted to the data of Sabourin et al. (1987) on mice and rats. The parameters were fixed to average values, except for the metabolic constants, which were optimized by non-linear regression. Travis et al. (1990) proposed a second model for mice, rats and humans. For the rat, Travis et al. used the experimental data of Sato et al. (1975), Rickert et al. (1979), Sato and Nakajima (1979), Snyder et al. (1981) and Sabourin et al. (1987). Fixed values were assigned to the physiological parameters, and the metabolic constants were interactively adjusted until a reasonable fit to the data was obtained. The third model, proposed by our group (Spear et al., 1990; Woodruff et al., 1989), was adjusted to the rat data of Rickert et al. (1979) and Sabourin et al. (1987; 1988). All the parameters were assigned ranges to account

for their biological variability and experimental uncertainty, and Monte Carlo simulations were performed to analyze the model behavior.

Each of the three models can reproduce the specific data to which it is fitted. The question remains, however, as to which parameter values are preferable, and what confidence should be given to the values used in one case or the other. Following standard statistical reasoning, and common sense, confidence is higher for those parameter values that lead to better fit to the available data. In the following, the goodness of fit of the models to the Fischer-344 rat data of Rickert et al. (1979) and Sabourin et al. (1987; 1988), which all three models can predict, is measured and discussed. We show that acceptable parameter values can be very different from standard ones while still being in a physiological range, and that using standard values does not ensure a good prediction of all tissue levels, independently of inter-species extrapolations. Finally, the usefulness of PBPK models for risk assessment is discussed.

METHODS

Models and parameter values

The model of Medinsky et al. (1989b; 1989c) includes four compartments: liver, fat, well and poorly perfused tissues. The equations used for the kinetics of benzene are similar to those given by Ramsey and Andersen (1984) or Gerlowski and Jain (1983). Both inhalation and gavage exposures can be handled by the model. Benzene metabolism is supposed to occur in the liver and is described by a Michaelis-Menten equation (Gerlowski and Jain, 1983; Michaelis and Menten, 1913). A description of secondary metabolism is included in the model. Secondary metabolism is not considered in our comparisons in order to keep the focus on the pharmacokinetics of benzene itself. Table 1 lists the parameter values used in Medinsky et al. model. Since the model was only fitted to experimental data of Sabourin et al. (1987), the total blood flow and the maximum rate of metabolism were scaled directly to body weight. To simulate the data of Rickert et al., in which the rats had different body weights, we scaled these parameter values, for Medinsky et al. model, to body weight to the 0.75 power. This is a widely accepted approach (Ramsey and Andersen, 1984), which is also used by Travis et al. (1990). In addition, we express the alveolar ventilation rate as a

Table 1: Parameter scaling coefficients[a] for the models of Medinsky et al. (1989b; 1989c) and Travis et al. (1990) and variation bounds used with Woodruff et al. (1989) model of benzene pharmacokinetics in the rat.

Parameter	Multiplier	Medinsky et al.	Travis et al.	Woodruff et al.
Uncertainty on body weight (∂Bw)[b]	-	0	0	-0.02 - 0.02
Scaling coefficients[b]				
sc1	1	0.75	0.75	0.65 - 0.85
sc2	1	0.75	0.75	0.65 - 0.85
Total blood flow (Ftot)	$(Bw+\partial Bw)^{sc1}$	0.237	0.205	0.22 - 0.28
Alveolar ventilation (Falv)	Ftot	1.67	1.41	0.50 - 1.00
Blood flows				
Liver (Fl)	Ftot	0.25	0.25	0.23 - 0.33
Bone marrow (Fbm)	Ftot	-[c]	0.039	0.01 - 0.05
Fat (Ff)	Ftot	0.09	0.09	0.04 - 0.10
Poorly perfused tissue (Fpp)	Ftot	0.15	0.11	0.10 - 0.18
Well perfused tissue (Fwp)	Ftot	0.51	0.51	-[d]
Volumes				
Liver (Vl)	$Bw+\partial Bw$	0.03	0.04	0.03 - 0.05
Bone marrow (Vbm)	$Bw+\partial Bw$	-[c]	0.03	0.02 - 0.04
Fat (Vf)	$Bw+\partial Bw$	0.11	0.07	0.07 - 0.13
Poorly perfused tissue (Vpp)	$Bw+\partial Bw$	0.66	0.11	-[e]
Well perfused tissue (Vwp)	$Bw+\partial Bw$	0.076	0.05	0.04 - 0.09
Blood/air partition coefficient (Pba)	1	18.0	15.0	10.0 - 26.0
Tissue/blood partition coefficient				
Liver (Plb)	1	1.0	1.13	0.5 - 3.0
Bone marrow (Pbmb)	1	-[c]	2.0	3.0 - 12.0
Fat (Pfb)	1	28.0	33.3	24.0 - 33.0
Poorly perfused tissue (Pppb)	1	0.6	1.0	0.6 - 2.0
Well perfused tissue (Pwpb)	1	1.0	1.13	0.5 - 3.0
Maximum rate of metabolism				
Liver ($Vmax_l$)	$(Bw+\partial Bw)^{sc2}$	0.0707	0.15	0.05 - 0.17
Bone marrow ($Vmax_{bm}$)	$Vmax_l$	-[c]	0.04	0.05 - 0.18
Vmax / Affinity constant ratio				
Liver ($Km_l/Vmax_l$)	1	0.618	0.35	0.02 - 0.8[f]
Bone marrow ($Km_{bm}/Vmax_{bm}$)	1	-[c]	0.35	0.001 - 0.2[f]
Intestinal Absorption rate (Aing)	1	0.00417	0.032	0.003 - 0.03

[a] Scaled parameter = multiplier × scaling coefficient. Units: Body weight in kg, flows in L/min, volumes in L, Vmax in mg/min, Km/Vmax in L/min, Aing in min^{-1}.

[b] This uncertainty factor is added to the body weight. The body weight was 0.225 kg in Rickert experiments and 0.29 kg in Sabourin experiments.

[c] This parameter is not in the model of Medinsky et al.

[d] Values for this parameter were computed at each run so that the sum of the flows was equal to 100% of the total flow.

[e] Values for this parameter were computed at each run so that the sum of the volumes was equal to 90% of the body volume.

[f] These parameters were sampled log-uniformly within the range, all others were sampled uniformly.

proportion of the total blood flow. These changes do not affect the results of the model simulations for the data of Sabourin et al., and the results are rigorously identical with those presented by Medinsky et al. The conversions simply allow an easier comparison of the parameter values for the three models.

The model of Travis et al. (1990) has the same structure except that it includes a bone-marrow compartment, where saturable metabolism can take place. The parameter values for this model are given in Table 1. Total blood flow and maximum rate of metabolism in liver and bone marrow are scaled to body weight to the 0.75 power. We express the alveolar ventilation rate in Travis et al. model as a proportion of the total blood flow. The conformity with Travis et al. (1990) simulation results was checked.

The model used by Woodruff et al. (1989) and Spear et al. (1990) is similar to the previous one. In addition, it describes the urinary elimination of the metabolites by a first-order process. Only the kinetics of benzene itself, and not the elimination of the metabolites, are considered in this paper. Table 1 gives the parameter ranges used in the model. Total blood flow, and maximum rate of metabolism in the liver and bone marrow are scaled to the body weight as in the above models. To maintain a ventilation over perfusion ratio of about 0.8 (Ramsey and Andersen, 1984), the alveolar ventilation rate is set to be proportional to the total blood flow. The proportionality constant was allowed to vary between 0.5 and 1.0. Earlier parameter adjustments (Bois et al., 1989b) showed that parameter values beyond the chosen ranges would not yield good fits to the data.

Monte Carlo simulations

The parameters in the model of Woodruff et al. are defined by their ranges. Consequently, there is an infinite number of possible values for each parameter, and the model predictions are statistical distributions rather than single points (Bois et al., 1989a; Bois et al., 1990; Farrar et al., 1989; Portier and Kaplan, 1989). Monte Carlo simulations are used to obtain a representative sample of these predictions. For a given Monte Carlo run each parameter value is randomly sampled from its range, and the simulation of all experimental data points is performed. The sampling of the parameter values is uniform, or log-uniform

when the ranges are large – so that low values are not under-represented. Such distributions make minimal assumptions about the location of the parameters. For the present study, one thousand simulations were performed.

Experimental data

The experimental data of Rickert et al. (1979) and Sabourin et al. (1987; 1988) were used. Both investigated the pharmacokinetics of benzene in male Fischer-344 rats. Rickert et al. (1979) exposed the rats to 490 ppm of benzene by inhalation for 6 or 8 hr. Blood, fat, bone marrow and liver levels were obtained at various times before and after exposure. After a 6-hr exposure the quantity of benzene remaining to be exhaled at several time points is also given by the authors. We considered data points only up to 9 hr after exposure for ease of computation (only three data points were left out). The data from Sabourin et al. (1987) provide more insight into the metabolic disposition of benzene. Fischer-344 rats were exposed by inhalation or gavage to various levels of the compound. The total amount of metabolites formed and the amount of benzene expired were recorded over 48 or 56 hr. In the study of Sabourin et al. (1988), 4 rats were exposed by inhalation to 50 ppm of benzene during 6 hr. The liver, lung and blood concentrations of benzene were obtained at the end of exposure.

Travis et al. (1990) fitted their model to the data described above, and to others obtained in Wistar and Sprague-Dawley rats. The latter are not considered here, given that the two other models were fitted to Fischer-344 rat data. The model of Medinsky et al. was not originally adjusted to the data of Rickert et al., but can be used to predict part of them. A difficulty arises, as bone marrow levels of benzene cannot be computed by that model. To make the model comparisons possible, two data sets are defined: 1. a "full data set", including all Rickert et al. and Sabourin et al. experimental results described above, 2. a "reduced data set" without the bone marrow data of Rickert et al. The full data set is used to compare the fit of Woodruff et al. and Travis et al. models, while the reduced data set is used to compare the three models all together.

Measure of goodness of fit

The log-likelihood of the data (Edward, 1972; Kalbfleisch, 1985) was used to measure the goodness of fit of the models of Medinsky et al. and Travis et al. The same measure was used to evaluate each Monte Carlo run of Woodruff et al. model. For each simulation the log-likelihood (LL) is given by:

$$LL = \sum_{i=1}^{N} -\frac{n_i}{2} \cdot \ln\left(1 + \frac{(y_i - \hat{y}_i)^2}{s_i^2}\right) \qquad (1)$$

where N is the number of mean experimental data points used ($N = 96$ in the full data set and 83 in the reduced data set); n_i and s_i^2 are respectively the number of experimental repetitions and the variance (with n_i degrees of freedom) for each data point; y_i is the experimental data point value, and $\hat{y}_i$ the corresponding model-predicted value (Edward, 1972, p.115-119). Practically, the log-likelihood is similar to a measure of the sum of squared deviates, weighted by the variance of each experimental data point. The higher the value of the log-likelihood, the better the fit.

RESULTS

Using the full experimental data set, which includes the data of Rickert et al. (1979) on benzene concentration in the bone marrow, the log-likelihood of the Travis et al. model is -326.1. Out of 1000 Monte Carlo simulations with Woodruff et al. model, 200 have a higher log-likelihood, and the best parameter set found has a log-likelihood of -262.1. With the reduced data set (i.e., without the bone marrow data), the model of Medinsky et al. has a log-likelihood of -404.8, while the model of Travis et al. has a log-likelihood of -317.0. Using the same data set and Woodruff et al. model, 971 out of 1000 runs have a higher log-likelihood (highest value: -200.8). The best Monte Carlo simulation for the full data set is also the second best for the reduced data set. Overall, the Monte Carlo runs produced 200 parameter sets simulating the data at least as well as either the Travis et al. or the Medinsky et al. models.

Figure 1 displays the values of the data points computed during the best Monte Carlo simulation, versus the actual experimental values of Rickert et al. (1979). On the same figure are also presented the values predicted by the models of Medinsky et al. and Travis et al. For a perfect fit to the experimental data all the

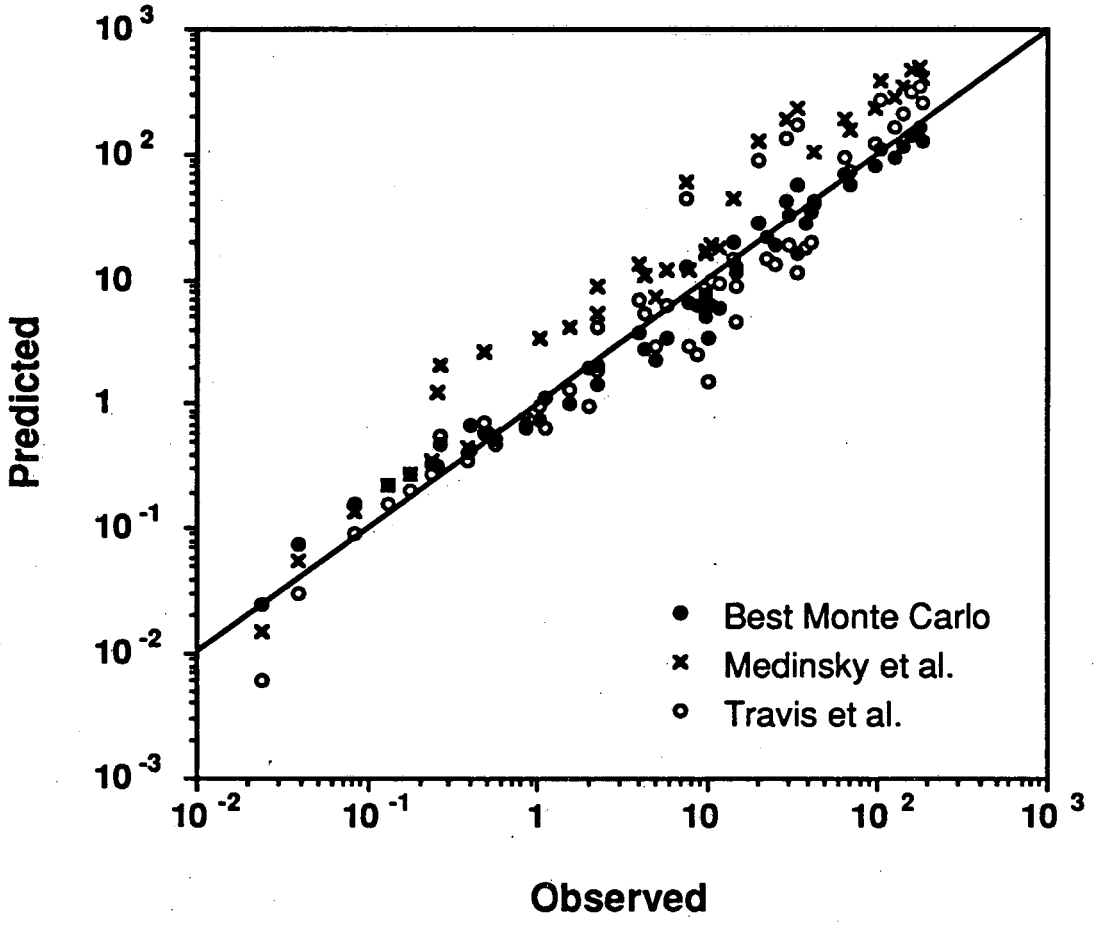

Figure 1: Predictions made using three published models, versus observed values of the data points obtained during Rickert et al. (1979) experiments. For a perfect fit, the points would fall on the identity line. The best Monte Carlo simulation lies the closest to the identity line.

points would fall on the "identity line" of the plot, each computed value being identical with its experimental counterpart. The spread of the points is the lowest for the best Monte Carlo simulation. The predictions made using Travis et al. model are more dispersed around the identity line, while with Medinsky et al. model the predictions almost always overestimate the data.

Figure 2 displays a similar comparison for the experimental data of Sabourin et al. (1987; 1988). The same comments as above apply, although the spread of the points obtained with the Travis et al. model is almost identical with the spread of the results of the best Monte Carlo simulation.

Figures 3 to 6 give examples of the simulation of individual data sets, using the three models. On these figures the shaded area contains the 200 best Monte Carlo simulations, the thick line represents the overall best simulation, while Medinsky et al. and Travis et al. model results are displayed in dashed lines. The overall best simulation does not always pass closer to individual data points than the model results of Medinsky et al. or Travis et al. For example, in Figure 5, Medinsky et al. and Travis et al. models simulate the data as well as the best Monte Carlo simulation does. It is only when all the experimental data are considered that the best Monte Carlo simulation is preferable. Table 2 gives the mean, standard deviation, upper and lower bounds, and best values for the parameters of the 200 Monte Carlo simulations of highest log-likelihood. The mean values are close to the center of the ranges, indicating that the distributions are symmetric within the ranges. As expected, the two exceptions are for the parameters sampled log-uniformly (Km_l and Km_{bm}). More significant are the differences between the standard deviations (expressed as a fraction of the range) and the theoretical value of $\sqrt{1/12}$ (≈ 0.29), obtained if the parameters were uniformly distributed. The lower the relative standard deviation of a parameter, the higher the information brought by the experimental data about that particular parameter. This leads to a ranking of the parameters where the most sensitive are $Vmax$ for the liver, the alveolar ventilation rate, the volume of the fat and the intestinal absorption rate. Some uncertainty, however, arises in this ranking from the fact that only 200 simulations are analyzed. Again Km_l and Km_{bm} should be excluded of the comparison because of their log-uniform original sampling.

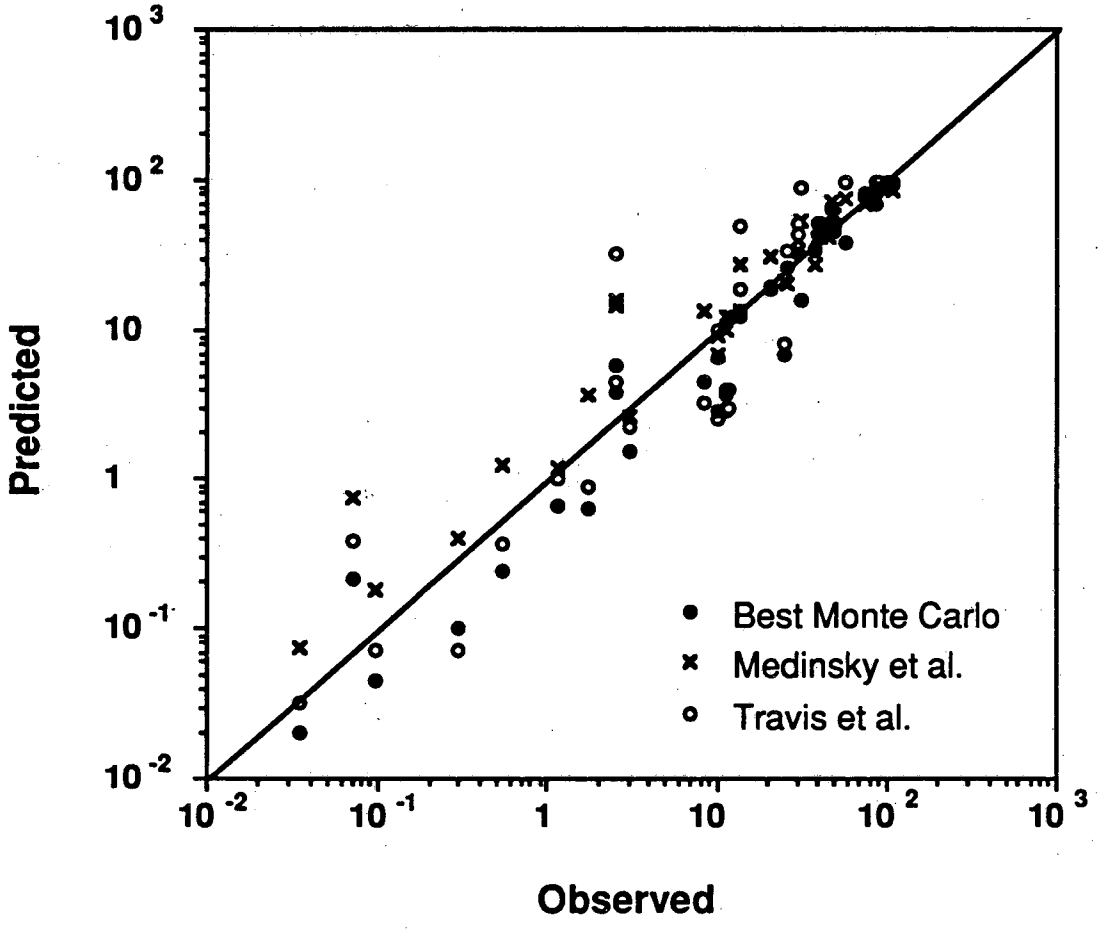

Figure 2: Predictions made using three published models, versus observed values of the data points obtained during Sabourin et al. (1987; 1988) experiments. For a perfect fit, the points would fall on the identity line.

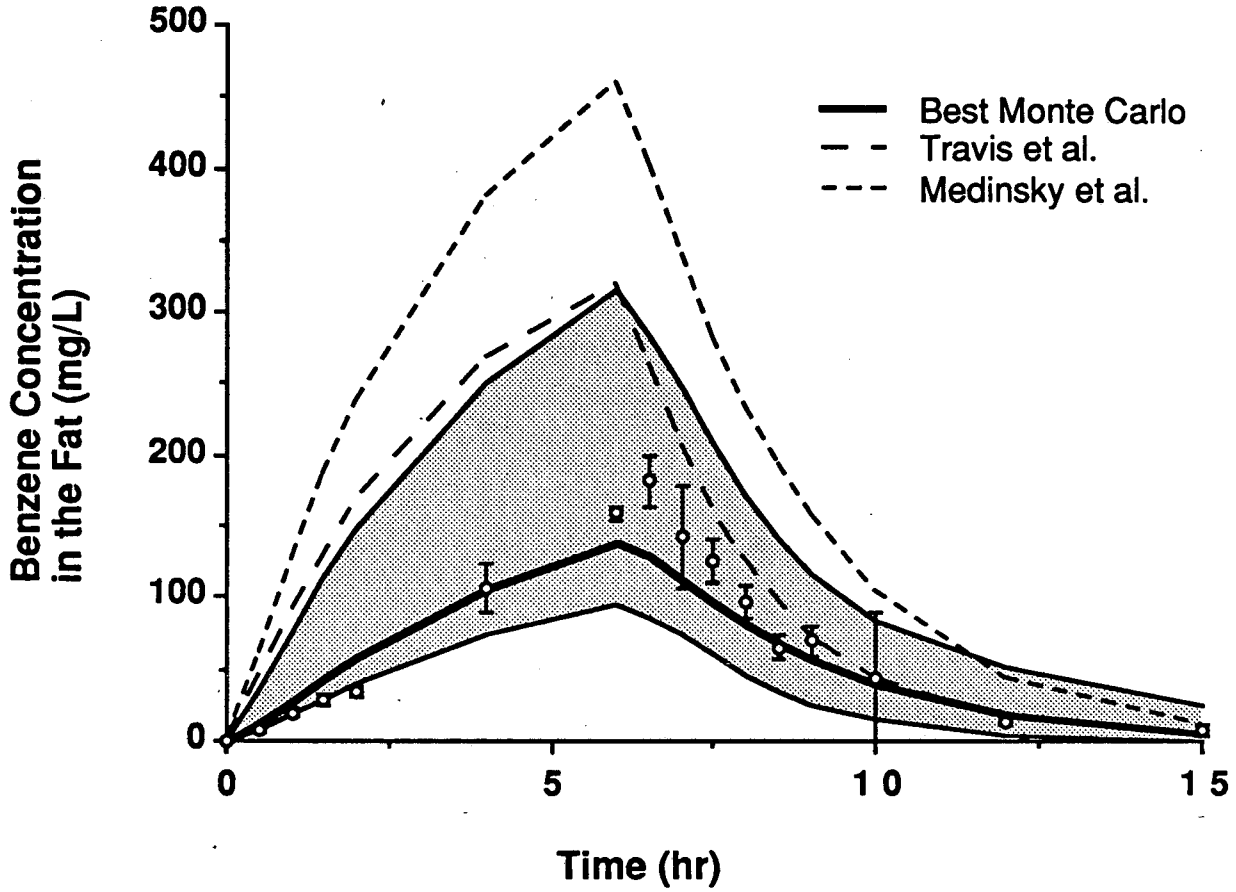

Figure 3: Benzene concentration in the fat of Fischer-344 rats, during and after a 6 hr exposure to 490 ppm benzene in the air. The open circles represent the experimental data (±sd) of Rickert et al. (1979). The time profiles obtained using three published models are given. The shaded area encloses the results of the 200 Monte Carlo simulations of highest log-likelihood.

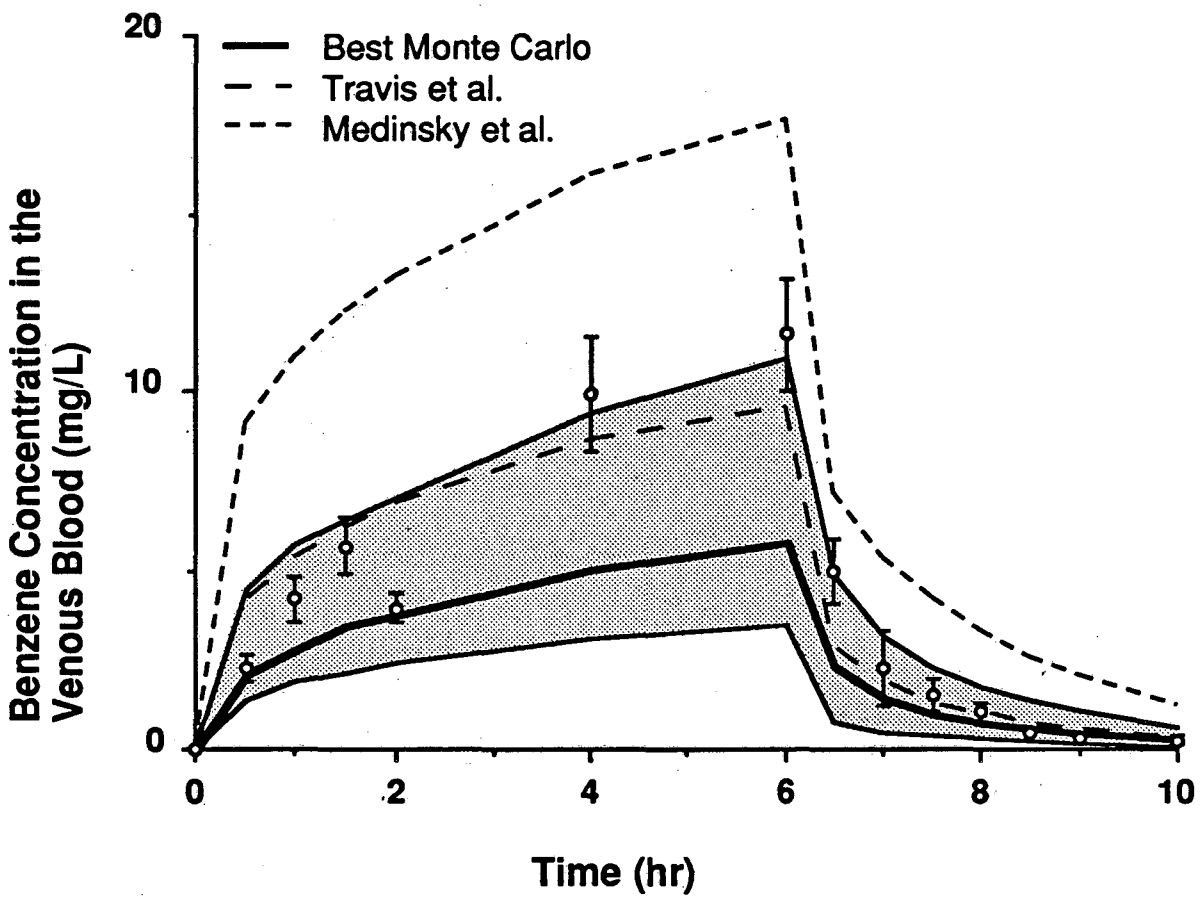

Figure 4: Benzene concentration in the venous blood of Fischer-344 rats, during and after a 6 hr exposure to 490 ppm benzene in the air. The open circles represent the experimental data (±sd) of Rickert et al. (1979). The time profiles obtained using three published models are given. The shaded area encloses the results of the 200 Monte Carlo simulations of highest log-likelihood.

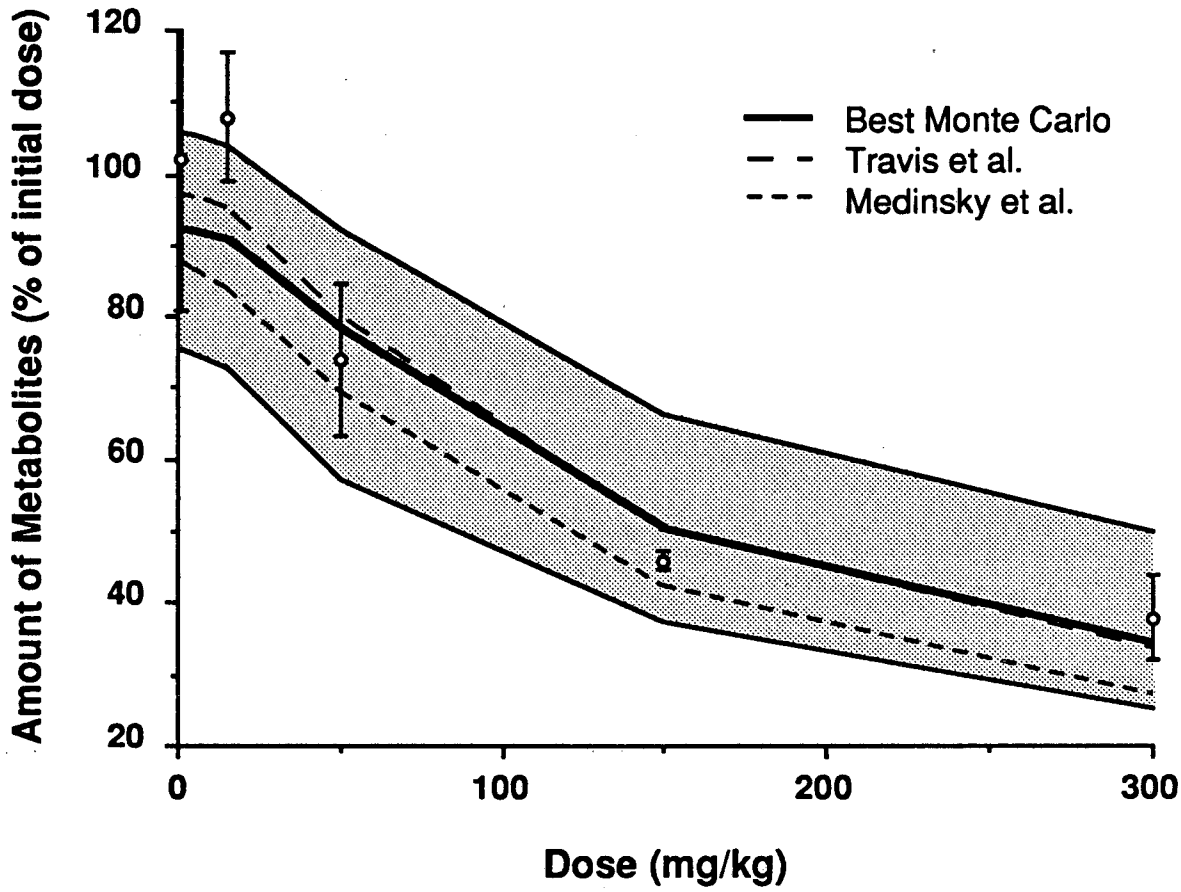

Figure 5: Percentage of the administered dose excreted as metabolites by Fischer-344 rats, during the 48 hours following benzene gavage. The open circles represent the experimental data (±sd) of Sabourin et al. (1987). The profiles obtained using three published models are given. The shaded area encloses the results of the 200 Monte Carlo simulations of highest log-likelihood.

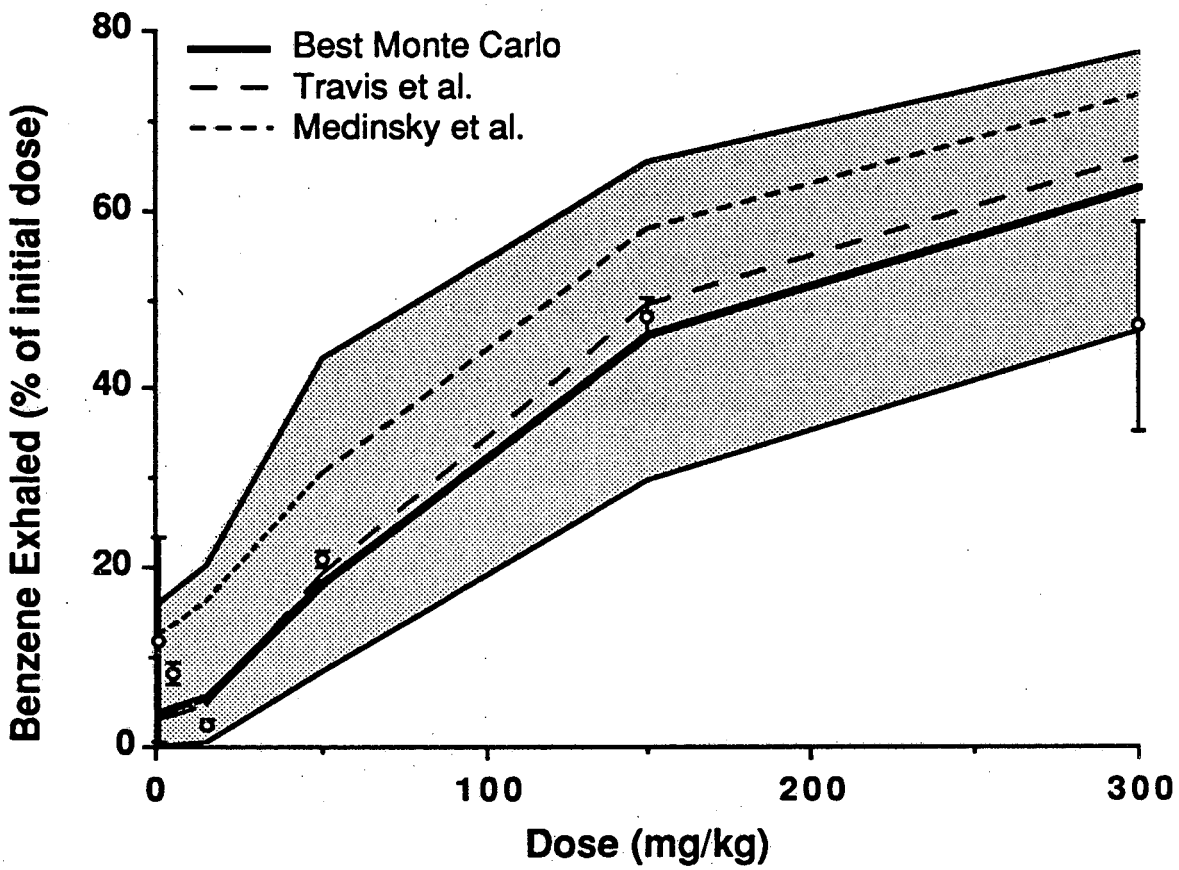

Figure 6: Percentage of the administered dose exhaled unchanged by Fischer-344 rats, during the 48 hours following benzene gavage. The open circles represent the experimental data (±sd) of Sabourin et al. (1987). The profiles obtained using three published models are given. The shaded area encloses the results of the 200 Monte Carlo simulations of highest log-likelihood.

Table 2: Mean, standard deviation, upper and lower bounds, and overall best value of the parameter scaling coefficients[a] obtained in the 200 best Monte Carlo simulations using Woodruff et al. (1989) model (see results section).

Parameter Name	Statistics for the Scaling Coefficient Values			
	Mean	S. D./Range[b]	Bounds	Best Value
Uncertainty on body weight (∂Bw)	0.000	0.275	-0.020 - 0.020	0.006
Scaling powers				
sc1	0.758	0.286	0.651 - 0.850	0.800
sc2	0.743	0.303	0.650 - 0.848	0.694
Total blood flow (Ftot)	0.250	0.283	0.220 - 0.280	0.251
Alveolar ventilation (Falv)	0.734	0.259	0.502 - 1.000	0.748
Blood flows				
Liver (Fl)	0.283	0.293	0.231 - 0.330	0.280
Bone marrow (Fbm)	0.031	0.275	0.010 - 0.050	0.040
Fat (Ff)	0.071	0.267	0.040 - 0.100	0.075
Poorly perfused tissue (Fpp)	0.141	0.288	0.100 - 0.180	0.150
Well perfused tissue[c] (Fwp)	-	-	-	-
Volumes				
Liver (Vl)	0.040	0.300	0.030 - 0.050	0.049
Bone marrow (Vbm)	0.030	0.300	0.020 - 0.040	0.023
Fat (Vf)	0.100	0.288	0.071 - 0.130	0.124
Poorly perfused tissue[c] (Vpp)	-	-	-	-
Well perfused tissue (Vwp)	0.067	0.300	0.040 - 0.090	0.090
Blood/air partition coefficient (Pba)	16.96	0.271	10.02 - 25.82	11.16
Tissue/blood partition coefficient				
Liver (Plb)	1.781	0.290	0.513 - 2.998	1.582
Bone marrow (Pbmb)	7.070	0.295	3.020 - 11.96	5.634
Fat (Pfb)	28.39	0.289	24.03 - 32.91	27.08
Poorly perfused tissue (Pppb)	1.258	0.281	0.607 - 1.991	1.991
Well perfused tissue (Pwpb)	1.715	0.281	0.510 - 2.979	2.698
Maximum rate of metabolism				
Liver ($Vmax_l$)	0.117	0.252	0.054 - 0.169	0.091
Bone marrow ($Vmax_{bm}$)	0.113	0.271	0.050 - 0.179	0.050
Affinity constant				
Liver (Km_l)	0.228	0.263	0.022 - 0.800	0.108
Bone marrow (Km_{bm})	0.036	0.241	0.001 - 0.200	0.026
Intestinal Absorption rate (Aing)	0.017	0.269	0.004 - 0.030	0.007

a See Table 1 for the definition of the scaling coefficients. Units: Body weight in kg, flows in L/min, volumes in L, Vmax in mg/min, Km in L/min, Aing in min^{-1}.

b The standard deviation is expressed as a fraction of the range – i.e S.D. / (lower bound - upper bound).

c Values for these parameters were computed at each run (see Table 1).

DISCUSSION

We have compared the fit of three PBPK models for benzene to the published data of Rickert et al. (1979) and of Sabourin et al. (1987; 1988). The issues of the goodness of fit of these models, their ability to perform predictions or extrapolations, and their usefulness in risk assessment, are discussed in the following.

PBPK model fitting

The best fit was obtained with the model of Woodruff et al. (1989), after Monte Carlo sampling of the parameter values. Out of 1000 Monte Carlo simulations, 200 provided better fits than the models of Travis et al. (1990) or Medinsky et al. (1989b; 1989c). By all current standards, these 200 simulations can then be considered acceptable, as are the results presented by Medinsky et al. or Travis et al. The parameter values giving acceptable fits (Table 2) are spread almost all over their physiological ranges (Table 1), and "good" parameter values can be very different from the "standard" or average values commonly used.

This result could be interpreted as an indication that the precise value of most parameters is unimportant. Insensitive parameters could be assigned any physiological value, since they do not affect the model results. To obtain good adjustments, the problem would thus be to identify the crucial parameters. Unfortunately, this is not as easy as it seems. The effort by Medinsky et al. (1989c) to improve the fit of their previously published model (Medinsky et al., 1989b) is, in this respect, instructive. In the latest report, the Michaelis-Menten parameters, *Vmax* and *Km*, for the metabolic clearance of benzene were fitted to Sabourin et al. data by least-square minimization (together with other parameters of the secondary metabolism, which have no impact on the results presented here). The revised *Vmax* and *Km* values are respectively two and five times smaller than their initial values, which had been empirically adjusted. Yet, this fitting of *Vmax* and *Km* is not sufficient to get good model predictions of Rickert et al. data. Travis et al. also varied the value of *Vmax* for the bone marrow to improve the fit to the data of Rickert et al. But this adjustment is limited to the bone marrow data, and does not consider the possibility of correlations with other parameters, such as the blood flow or the partition coefficient in the tissue. The problem is that with many parameters and rela-

tively few data points, the correlations between all parameters are large, and the parameters covary extensively (Spear et al., 1990). The identification of the crucial parameters is therefore difficult. In brief, the fact that the models of Medinsky et al. or Travis et al. do not yield the best fits shows that adjusting the metabolic parameters is not sufficient. To significantly improve the fit it is necessary to optimize the other parameters as well.

With PBPK models, only a few parameters are usually adjusted because full parameter optimization by standard "hill climbing" methods is time consuming, expensive or simply unfeasible with such large models. While standard optimization methods have limited power in dealing with PBPK models, Monte Carlo simulations give many acceptable fits, and do not constrain the parameters to fixed values. However, due to their randomness, Monte Carlo simulations do not lead automatically to the absolute best fit. The best fit and parameter values obtained with 1000 simulations (Table 2) may be quite different from the overall maximum-likelihood ones, if the latter were computable. There is room for improvement in the best fit found, as several predictions are nearly an order of magnitude away from the observed values (Figures 1 and 2). It should be also noted that biological experiments performed only in triplicate cannot lead to very accurate estimates of the underlying parameters. The reader is referred to a recent paper by Hattis et al. (1990) for a further discussion of these issues.

Accuracy of extrapolations

As expected, most of the poor agreements obtained with the models concern data points to which they were not fitted. For example, with the model of Travis et al., the concentration of benzene in the fat compartment is poorly predicted. The model of Medinsky et al. does not simulate very well the data of Rickert et al. or the quantity of benzene exhaled during the gavage experiments of Sabourin et al. (Figures 3, 4 and 6).

These disagreements with the experimental data raise some doubts about the ability of PBPK models to extrapolate correctly to experimental conditions different from the ones to which they are fitted. These models are often presented as solutions to extrapolation problems. In fact, most of the time parameters have

to be modified to give acceptable results, and blind model predictions are not guaranteed to give good results when compared with the data.

Another possibility, when confronted with poor model predictions, is that part of the experimental data is wrong. For example, the reported levels of benzene in the fat could be underestimates, some benzene having possibly been lost during the tissue collection. The problem is that rejecting data points, or whole data sets, on the basis of the model's fit, requires far more statistical confidence in the parameter values and quality of the fit than is currently achievable with such large models. On the basis of Medinsky et al. or Travis et al. model fits it might be tempting to reject the fat tissue data, but the best fit so far, obtained by Monte Carlo simulations, predicts these data quite well (Figure 3).

PBPK models and cancer risk assessment

As often with PBPK models, one of the long-term goal of modeling benzene toxicokinetic is cancer risk assessment (Medinsky et al., 1989a; 1989c). It is reasonable to assume that Medinsky et al. focused on correctly fitting the quantity of metabolites formed because these metabolites are likely to be the ultimate agents of benzene carcinogenicity (Eastmond et al., 1987; Kalf, 1987). This is at the expense of a good adjustment to the data of Rickert et al. on the kinetics of benzene itself. Such a lack of fit could be a problem if untransformed benzene were to play a role in the carcinogenicity of benzene, as suggested by Lee et al. (1988), or if other end-points than carcinogenicity were investigated. On the other hand, if benzene metabolites are the effective carcinogens, the need for a detailed physiological description of benzene kinetics is questionable. In animals, direct measurements are available on the amounts of metabolites formed after various routes of administration (Sabourin et al., 1987; 1988; 1989). In cases where the dose-measure chosen is simply the amount metabolized, it seems more profitable to fit a one compartment model with a Michaelis-Menten term to the data on metabolism (Bailer and Hoel, 1989; Beliles and Totman,

1989). Given the current lack of understanding of the exact role of individual metabolites in benzene carcinogenicity, a simple approach might be sufficient for regulatory risk assessment purposes. We propose that extensive descriptions of benzene kinetics and metabolism are, for now, warranted only when the mechanism of its toxicity is investigated.

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