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Benzene Toxicokinetics in Humans
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Bone Marrow Exposure to Metabolites

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ABSTRACT

A three compartment physiologically-based toxicokinetic model was fitted to human data on benzene disposition. Two separate groups of model parametrizations were obtained, depending on which data sets were being fitted. The model was then used to simulate five scenarios of environmental or occupational exposures. Predicted values of the total bone marrow exposure to benzene and cumulative quantity of metabolites produced by the bone marrow were generated for each scenario. The relationship between cumulative quantity of metabolites produced by the bone marrow and continuous benzene exposure was also investigated in detail for simulated inhalation exposure concentrations ranging from 0.0039 ppm to 150 ppm.

At the level of environmental exposures, no dose-rate effect was found for either model parametrization. The occupational exposures lead to only slight dose-rate effects. A 32 ppm exposure for 15 minutes predicted consistently higher values than a 1 ppm exposure for 8 hours for the total exposure of bone marrow to benzene and the cumulative quantity of metabolites produced by the bone marrow. The general relationship between the cumulative quantity of metabolites produced by the bone marrow and the inhalation concentration of benzene is not linear. An inflection point exists in some cases leading to a slight S-shaped curve. At environmental levels (0.0039 - 10 ppm), the curve bends upward, while it saturates at high experimental exposures (greater than 100 ppm).

INTRODUCTION

Benzene, a human carcinogen, is ubiquitous in the human environment. Workers in the petroleum, petrochemical and other related industries are exposed via inhalation to benzene concentrations on the order of a part per million (ppm).[1-5] The general population is widely exposed to benzene in the atmosphere due to volatilization of gasoline, exhaust pipe emissions from motor vehicles and emissions from other combustion sources. These exposures are typically at the part per billion level.[6, 7] Both workers and the general population are also exposed to benzene from cigarettes, either directly through smoking or indirectly from tobacco smoke in the environment. Within both populations, exposures can be nearly continuous or can involve intermittent peaks against some background level.

Estimates of the risks of benzene exposures to the general population are based on relatively simple extrapolations from high level exposures. However, relationships between exposure and tissue dose (and risk) can be nonlinear if saturable metabolic processes are involved. In such a case, using the external exposure to the parent compound is incorrect. Physiologically-based toxicokinetic (PBTK) models can provide more accurate estimates of risks by predicting tissue exposure to the active compound(s).

Many of the published experimental studies describe attempts to fit linear or compartmental toxicokinetic models to benzene toxicokinetic data. Recently, Travis et al.[8] developed a physiologically-based toxicokinetic model for benzene in humans. However, no formal model parametrization was performed by Travis et al. Reference values were used for most of the model parameters. The metabolic parameters were then adjusted to visually fit the data. In contrast, in the work reported here, an attempt is made to formally fit a physiologically-based toxicokinetic model. Multiple parameter sets were obtained that fit the data. These parameter sets were then used to investigate the toxicokinetics of benzene for realistic (environmental and occupational) exposure scenarios, focusing particularly on dose-rate effects. One benefit of using a physiological model is that it is reasonable to expect that extrapolations of such a model have more basis in reality than a purely empirical model. If the quantity of metabolites produced in the bone marrow, is the relevant measure upon which leukemia risk estimates should be based, it is useful to have the relationship between such a quantity and the exposure concentration. Thus, target site exposures, difficult to measure experimentally, were also determined by simulation for a wide range of inhalation concentrations.

METHODS

Experimental Data

Data from four inhalation exposure studies were used to fit the model. Teisinger and Fiserova-Bergerova,[9] as reported by Docter and Zielhuis,[10] measured urinary phenol and its conjugates during and after exposure to 25 ppm of benzene for 8 hours. The results are for a single individual, but this is not clearly indicated.

Srbova et al.[11] made measurements in 23 individuals, but reported the expired air and venous blood concentrations in only one subject during a 90 minute exposure and up to 6.5 hours postexposure. The average benzene exposure concentration was approximately 98 ppm. However, the exact exposure concentrations reported at 15 minute intervals were used in the simulations.

Data reported by Sato et al.[12] for the average end-tidal air and venous blood concentrations for three male subjects were also used. The exposure benzene concentration was 25 ppm for a duration of two hours. The postexposure measurements were made for up to 5 hours. A second paper by Sato et al.[13] reported the mean and standard deviation of benzene in end-tidal air and venous blood concentrations after exposure to 25 ppm for two hours. The results were reported for five males and five females separately. The end-tidal air measurements were made up to five hours after the exposure. Venous blood measurements were made both during and after exposure.

In the following, these studies are coded as "T" for Teisinger and Fiserova-Bergerova,[9] "Sr" for Srbova et al.,[11] "Sa74" for Sato et al.,[12] and "Sa75" for Sato et al.[13] The Sato et al.[13] results are treated as two separate experiments (males and females) for a total of five experiments used in the model parametrization.

Model Structure and Parametrization

A physiologically-based toxicokinetic model, previously validated[14], was fitted to benzene concentrations in expired air and venous blood, and urinary phenol data. The model includes three compartments: central, bone marrow and fat tissue compartment. Inhalation or ingestion exposures can be simulated. Benzene is eliminated by exhalation or via saturable (Michaelis-Menten) metabolism in the central and bone marrow compartments. The model requires the definition of 16 physiological variables calculated from their associated scaling coefficients. The sampling ranges of the scaling coefficients, hereafter referred to as parameters, are given in Table 1. For fitting, the Monte Carlo technique of Spear et al.[14-16] was used. In a given Monte Carlo simulation, the parameters were selected randomly from uniform or log-uniform distributions. The system of equations describing the model was solved numerically to make predictions for each criterion and the quality of the fit was assessed. The fit was declared acceptable if all predicted values (concentrations or metabolite amounts) were within ±50% of the

corresponding published data value. Three to four experimental data points were chosen to summarize the time course of measurements made during exposure and after exposure. A table of the criteria is available upon request. The parameter sets yielding good fits (i.e. meeting these criteria) were saved and labeled "PASS" parameter sets.

To improve sampling efficiency (i.e. finding "PASSes"), 3000 preliminary simulations were performed. From these 3000 runs, PASS parameter sets providing good fits to the data for each of the five experiments, considered individually, were extracted. The bounds of the parameter ranges (i.e. the lowest and the highest "PASS" parameter values) were determined. The intersection of the five experiments' PASS parameter ranges was used for the parameter sampling in the subsequent Monte Carlo runs. Simulations were performed until 20 PASS parameter sets were found.

A cluster analysis[17] was performed on the final PASS parameter sets obtained through Monte Carlo simulations to verify whether or not they were connected in the parameter space, and thus formed one set of solutions.

Exposure Scenarios

After parameterizing the model, simulations were performed to predict the quantity of metabolites produced in bone marrow (Qmet_bm), over 1 week, at steady-state for various exposure scenarios. Predictions over the same week were also made for the integral of the concentration of benzene in bone marrow versus time curve (AUC) which represents the total exposure of the bone marrow to benzene. Five realistic exposure scenarios were developed for the general population (ppb exposures) and for a worker population (ppm exposures). These were selected to represent a wide range of exposures, from the average population exposure, to the occupational exposure at the current standards. For the general population, continuous and intermittent peak exposure scenarios which provided the same total inhalation dose were constructed (scenarios I and II in Table 3). An air concentration of 0.0039 ppm benzene was assumed for the "continuous background" exposure scenario. This concentration is approximately the 80th percentile of the personal exposures measured for 50 people in Los Angeles in May, 1984.[6] These 50 subjects were randomly selected to represent a population of 330,000 residents of the South Bay section of Los Angeles.

The second intermittent exposure scenario, the "gasoline pumping" scenario, assumes a continuous background exposure of 0.0036 ppm benzene in air. This scenario models a subject refueling his/her automobile with unleaded gasoline at 7 a.m. on Monday and 7 p.m. on Thursday. The refueling process lasts 15 minutes and the average concentration of benzene in air is 0.092 ppm. This concentration was the geometric mean of the benzene concentrations measured for short term personal air samples for service station attendants in three locations in the United States.[7]

The third scenario, encountered by some members of the general population, was based on benzene exposures of a light smoker (i.e. 6 cigarettes per day) representing a total inhalation target dose of 300 μg/day. Mainstream cigarette smoke provides a benzene dose of about 50 μg/cigarette based on

measurements of mainstream emissions of 1R4F cigarettes, a reference cigarette.[18, 19] This scenario assumes a continuous background concentration of 0.00062 ppm benzene in air which is at about the 10th percentile of the personal exposures measured for Los Angeles residents in May, 1984.[6] Against that background, the smoker was assumed to smoke 6 cigarettes per day - 2 at 6 a.m., at noon and at 6 p.m., 10 minutes exposure per cigarette, 50 μg benzene per cigarette.

For the worker population, a continuous exposure of 1 ppm over an 8 hour work day and a peak 32 ppm exposure for 15 minutes per day were selected (scenarios IV and V in Table 3). These scenarios yields the same total exposure (480 ppm×min). The 1 ppm exposure is the current OSHA permissible exposure level (PEL). Note that the 32 ppm, 15 minutes, exposure would be in violation of the OSHA short term exposure level (STEL) of 5 ppm for 15 minutes.

Cumulative Quantity of Metabolites vs. Inhalation Concentration of Benzene

After parametrization to data from exposures of 25 and 98 ppm benzene, our model was used to make predictions of Qmet_bm at lower and higher exposure concentrations. These concentrations ranged from 0.0039 to 150 ppm and were simulated as continuous exposures.

RESULTS

Parametrization

Parameter sets producing simulation results which pass all the goodness-of-fit criteria were not found. Two groups of parameter sets were obtained: one which fit both T and Sr data; and another group fitting Sa74 and Sa75 data. When the T-Sr PASS parameter sets are used to simulate the Sa74-Sa75 data, four predicted values are always below the ±50% criteria bounds. Similarly, when the Sa74-Sa75 PASS parameter sets are used to simulate the T-Sr data, three predicted values are always too high. The cluster analysis confirmed this result. Nearly 2.7 million simulations were needed to find 20 parameter sets fitting the T-Sr data. Fitting Sa74 and Sa75 was a bit easier. About 500,000 runs were needed to obtain 20 passing parameter sets.

Figure 1A shows the 20 predicted versus observed values for all T-Sr data, using the model fits to these data (the data represent different measurements expressed in different units). A perfect fit to the data would have all the points on the diagonal (y=x). Figure 1B shows the 20 predictions for all Sa74 an Sa75 data, using the model fits to these data.

Exposure Scenario Simulations

Figures 2A and 2B plot Qmet_bm for exposure scenarios I-V. A set of connected markers represents the output from the model using one PASS parameter set. Exposure scenarios I and II have the same exposure time weighted average (TWA) and identical results predicted for Qmet_bm, thus no dose-rate effects occur. The Qmet_bm for exposure V is consistently higher than the Qmet_bm values for exposure IV. The relative differences range from 0.13 to 4.6 percent (predictions from both T-Sr and Sa74-Sa75 parametrizations). The predictions for AUC followed similar trends. No difference was seen between the AUC for exposures I and II. The relative differences for exposures IV and V ranged from 0.20 to 11 percent based on predictions from both parametrizations, therefore showing slight exposure rate effects.

Cumulative Quantity of Metabolites vs. Inhalation Concentration of Benzene

Figure 3 is a plot of Qmet_bm versus exposure concentration generated by the first five parameter sets fitting Sa74-Sa75 data. Of the 20 parameter sets, eleven sets generate S-shaped curves like runs 1 and 2. Four curves look like run 3 which increases more than linearly with concentration. The rest look like curves 4 and 5 where no observable S-shape exists and saturation is beginning. Of the 20 curves generated by T-Sr parameter sets, eight curves look like runs 1 and 2, two curves look like run 3, and seven curves behave like runs 4 and 5. In this group there were three parameter sets which generate seemingly straight lines over the range of concentrations studied. Figure 4 plots the slopes calculated between adjacent points versus the mean inhalation concentration between the two points. From this plot it is clear that at low concentrations (< 50 ppm) the quantity of metabolite produced increases disproportionately with exposure concentration (increasing or decreasing slopes seen in Fig 4). Run 2, for example, predicts Qmet_bm equal to 0.114 mg/week at 0.005 ppm. At a concentration of 50 ppm, Qmet_bm is 1494 mg/week. Above 50 ppm, the slope decreases slightly in most cases. Run 2 is an extreme case where the saturation effect at high dose is clear and the slope goes to zero above 150 ppm.

We attempted to analytically derive the functional relationship between the rate of metabolite production by the bone marrow and the input concentration at steady-state. Yet, due to the complexity of the system we were unable to obtain an explicit solution (even with the help of symbolic manipulation programs such as Mathematica™ and Maxima™). However, a numerical solution was obtained which verified the accuracy of the numbers computed by integration to ±0.33%.

DISCUSSION

Experimental studies[9, 11-13, 20-27] usually involve high exposure concentrations relative to what is encountered in the environment. This is necessary to detect benzene concentrations in the blood and exhaled air of the subjects when assay sensitivity is low. The quantities typically measured in human studies are the benzene concentrations in venous blood and expired air, and the concentration of phenol in urine. The four studies[9, 11-13] used in this investigation were selected from the body of human data because we judged their reports to be the most complete in terms of exposure procedure and reliable analytical methods.

Occupational studies[1-5] are more "realistic" than experimental studies, but uncontrollable factors (e.g. fluctuating and uncertain exposure concentration and differences in activity levels) make these data more uncertain. The measured quantities are usually the same as in an experimental study, but with fewer and unevenly spread data points over time. For these reasons, analysis of these data, and in particular modeling them for prediction purposes, is difficult and may yield results with greater uncertainty and variability than modeling experimental studies. We therefore did not use data from occupational studies.

Model Structure and Parametrization

Two distinct sets of data lead to two different parametrizations of the model. Therefore the two groups of data: Group 1 consisting of T and Sr; and Group 2 consisting of Sa74 and Sa75 appear to be incompatible. In terms of model parameters this translates into significantly different values for some of them. Table 2 shows that the univariate ranges obtained do not overlap for the blood to air partition coefficient. In addition, it is very likely that high dimensional correlation between parameters exists, distinguishing one PASS region from the other.

It is interesting that for both sets of parameters, the central compartment tissue to blood partition coefficient, PCb_cen, must fall in the range of 2.00 to 2.63 for both groups. This range covers only 7% of the sampled range. A true test of the model would be experimental verification of this result. Homogenized rabbit tissue to blood partition coefficients, for some of the tissues included in the central compartment, range from 1.08 to 1.93,[12] a narrow range, but specific human values are unavailable.

The cause of the disparity between the two groups of model parametrizations is unclear. Some possibilities include: 1) the data simply represent two different underlying populations; 2) some measurements are poor or biased; 3) unreported differences in the experimental procedures exist; 4) the model structure is inadequate to describe the system dynamics; and 5) the bounds for the criteria do not adequately account for the measurement uncertainty and interindividual variability.

If the model structure is correct, then some conclusions about the data can be reached. First, the differences in the blood to air partition coefficient could be indicative of pharmacogenetic differences in the subjects. Sato et al.[12, 13] conducted their experiments in Japan, while the T and Sr experiments were performed in Czechoslovakia. Pharmacogenetic differences in the subjects could be responsible for the way

in which benzene was absorbed, metabolized, and/or eliminated. Second, changes in the analytical measurement technology over the 20 year period, or the different techniques employed by the researchers could also account for the disparate parametrizations. However, we have carefully reviewed the measurement and experimental procedures and see no obvious differences that would account for the two parametrizations.

There is always the possibility that the model structure is inadequate and validation of this model as a reliable predictor can only take place when additional data become available. For now, one can only postulate the meaning(s) of the results presented here. In previous work[8, 28-31] the toxicokinetic models were considered valid if they were able to visually fit the data. These models were used for risk assessment[30, 31] although they were not validated with data pertaining to the quantity of interest. In this context the model presented here is of comparable quality.

The implication for risk assessment is that one should compare systematically the fits and model predictions obtained with different studies. This implies that the models should be formally fitted, using statistical techniques (e.g. Monte Carlo simulations). Statistical fitting also yields confidence bounds around model predictions, which should be a standard output of risk assessment.

Criteria and Their Meaning

Confidence bounds, or more generally the distribution of predictions, represent several nested levels of variability: at least, analytical measurement errors, intrasubject variability, and intersubject variability. It would be very useful to have an estimate of population variability, in order to judge whether results obtained in a Japanese study can be used for a Czechoslovakian population, for example. Yet, physiologically-based models previously developed for the purpose of predicting doses to target tissues do not try to account for population variability. We propose that, if the criteria for goodness of fit, as we define and use them here, account for measurement uncertainty and population variability, then both these effects are captured by the set of model parametrizations satisfying the criteria. As a consequence, each parametrization can be thought of as representing a possible member of the human population. The Monte Carlo method used here can therefore be presented as a "population toxicokinetic" approach.

The criteria were chosen to allow for population variability and uncertainty in the data. Sato et al.[13] reported standard deviations for their data. However, since this information was not available for all of the data, a standard, ±50%, was used. This is an underestimate of the variability in the urinary phenol data since Teisinger and Fiserova-Bergerova reported five-fold differences in values across individuals. For the end-tidal air and blood benzene concentrations reported by Sato et al.[13], ±50% of the measured value is generally greater than two standard deviations of the mean for five individuals.

To assess the robustness of our findings, in particular the existence of two groups of data sets, with respect to the definition of the criteria, we attempted to fit the model across all data sets (T, Sr, Sa74, and Sa75) while removing three points which were less than a factor two above the reported analytical detection

limits. No PASS point for these new criteria was found by Monte Carlo sampling (1,250,000 simulations) and the clustering analysis again found two clusters.

Simulation Results

Exposure rates are important to consider in regulatory policy because high exposure concentrations for short periods of time could result in different toxic effects than low exposures over long periods of time. Different rates of exposure were simulated to see if there was any difference in the predicted value for Qmet or AUC of benzene in bone marrow. Since saturable reaction kinetics are known to describe the metabolism of benzene in the bone marrow and central compartments, it is possible that high concentrations for short periods of time could saturate the metabolic process, thereby producing dose-rate effects.

For environmental exposures no dose-rate effect was seen in the predictions of primary metabolites or for the benzene AUC in bone marrow. A slight but consistent dose-rate effect appears at the level of occupational exposures (scenarios IV and V). The possibility of not having reached steady-state for exposure scenario IV was investigated by performing simulations up to five weeks. (Since this scenario predicts the smaller values, not having reached steady-state means that benzene is still accumulating in the bone marrow. The predicted values would only increase for exposure scenario V if it was not at steady-state after three weeks.) The predicted values between the fourth and fifth week were the same as those reported between the second and third.

The model fitted to the Sa74-Sa75 data yields predictions of Qmet_bm with less variability than the model fitted to the T-Sr data. The distribution of these predictions appears close to log-uniform. On the other hand, more variability was found in the prediction of AUCb_bm from the Sa74-Sa75 parameter sets. The predictions from both parametrizations appear to be uniformly distributed for AUCb_bm. Although two distinct sets of model parametrizations were found, the predictions from both sets at low exposure concentration are similar (Figures 2A & 2B).

The predictions of Qmet made by both parametrizations of the model are different from the findings of Bois and Paxman[32] for rats exposed to benzene. In rats, no dose-rate effects were found at the primary metabolite level which we studied here. However, at the level of individual metabolites, important dose-rate effects were observed. Slight dose-rate effects are already present in the disposition of primary metabolites in humans. These may not be biologically significant by themselves, but it can be suspected that individual active secondary metabolites are even more affected, with possibly a large impact on cancer risk. In this context, the application of a Short Term Exposure Limit for benzene seems warranted, even if it is difficult to assess whether its current value (5 ppm for 15 minutes) is over- or under-protective. More data on human metabolism of benzene is needed to precisely answer this question.

For continuous exposures, Qmet_bm predictions by Sa74-Sa75 parameter sets are generally greater than the predictions made by T-Sr parameter sets. Of the 20 Sa74-Sa75 predicted curves, 9 of them

showed generation of metabolites in excess of 1500 mg/week within the exposure concentrations studied. Only one out of 20 T-Sr curves showed production of metabolites in excess of 1500 mg/week.

Variability is not only present between the two groups of parametrizations, but also within each group. Thinking of each parametrization as a possible member of the population, we see that some individuals exhibit saturation of the production of metabolites in bone marrow, while others increase linearly or superlinearly. In the group of individuals represented by the Sa74-Sa75 parametrizations, an exposure of 25 ppm produces a 9 fold difference between the highest and lowest Qmet_bm. There is a 24 fold difference in the T-Sr results at the same exposure concentration.

In recent risk assessments, it has been assumed that simple Michaelis-Menten kinetics describe correctly the relationship between the applied dose and the milligram equivalents of benzene metabolized[33, 34] per unit time. This study shows that Michaelis-Menten kinetics do not describe the relationship at the site of action, the bone marrow. How, then, do we best extrapolate the high dose data to low doses in this context? The best approach should be the use of a general model, similar to ours, which can characterize the range of individual responses. A Michaelis-Menten approximation is easy to fit and would be appropriate for some individuals, but not for all. There is no guarantee that using a simple Michaelis-Menten relationship is even correct for extrapolating the population average. Using average data to perform cancer risk assessments should actually be avoided.

The findings described here: dose-rate effects at occupational dose levels, S-shape form of the production of metabolites as a function of exposure concentrations, large interindividual variability, by their potential importance for human risk assessment of benzene induced leukemia, deserve further attention. The recent publication of a new set of data[27] offers the potential for an independent verification of these results. In addition, attempts are being made to acquire the missing information which made some of the older published reports unsuitable for this modeling investigation.

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Table 1: Physiological variables and their scaling coefficients (SC) for benzene toxicokinetics in humans, with the corresponding initial Monte Carlo sampling ranges[a, b].

Physiological Variable	SC	Multiplier	SC Lower Bound	SC Upper Bound
Cardiac output	Sc_Flow_tot	$BW^{0.75}$	0.188	0.543
Alveolar ventilation	VPerf_Rat	cardiac output	0.500	1.50
Blood flows				
Bone marrow	Flow_bm	cardiac output	0.00821	0.0665
Fat	Flow_fat	cardiac output	0.0203	0.0784
Central compartment	Flow_cen	cardiac output	-[c]	-[c]
Volumes				
Bone marrow	V_bm	BW	0.010	0.060
Fat	V_fat	BW	0.109	0.337
Central compartment	V_cen	BW	-[d]	-[d]
Blood/air partition coefficient	PCb_art	1	1.66	17.9
Tissue/blood partition coefficients				
Bone marrow	PCb_bm	1	3.03	29.3
Fat	PCb_fat	1	23.0	70.5
Central compartment	PCb_cen	1	2.02	20.1
Maximum rate of metabolism, Vmax				
Central compartment	Vab_cen	$BW^{0.75}$	0.00104	0.170
Bone marrow	Vab_bm	Vab_cen	0.020	0.300
Vmax/Km ratios				
Central compartment[e]	Kab_cen	1	0.00533	0.362
Bone marrow[e]	Kab_bm	1	0.000358	0.495
Elimination rate constant	Km_out	1	0.000211	0.0028
Fraction of metabolites excreted as phenol or phenol conjugates	PhFraction	1	0.600	1.00

[a] Physiological parameter = scaling coefficient × multiplier. Units: BW = body weight in kg, flows in L/min, volumes in L, Vmax in mg/min, Vmax/Km in 1/min.

[b] Initial lower bounds and upper bounds were obtained from the literature or scaled from animals. All scaling coefficients were sampled from uniform prior distributions except where otherwise noted.

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

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

[e] The variable was sampled using a log uniform distribution (i.e., uniformly sampled after log transformation).

Table 2: Parameter range results obtained from the Monte Carlo sampling[a].

	T-Sr Experiments[b]		Sa74-Sa75 Experiments[c]	
Scaling Coefficient	Lower Bound	Upper Bound	Lower Bound	Upper Bound
Sc_Flow_tot	0.297	0.477	0.38	0.52
VPerf_Rat	0.547	1.08	0.725	1.17
Flow_bm	0.00969	0.0613	0.015	0.0612
Flow_fat	0.0504	0.0759	0.0531	0.0757
V_bm	0.0193	0.0592	0.0231	0.0587
V_fat	0.138	0.313	0.125	0.31
PCb_art	6.5	10.9	12	17.1
PCb_bm	6.31	27.1	5.14	27.3
PCb_fat	25.4	68	24.2	61.9
PCb_cen	2.02	2.62	2.01	2.63
Vab_cen	0.017	0.168	0.0316	0.167
Vab_bm	0.0452	0.271	0.0528	0.281
Kab_cen	0.00778	0.0169	0.0113	0.0209
Kab_bm[d]	0.000475	0.128	0.000505	0.0804
Km_out	0.0022	0.00268	0.000996	0.00263
PhFraction	0.607	0.786	0.624	0.956

[a] Sampled uniformly except where otherwise noted.
[b] T-Sr: Teisinger and Fiserova-Bergerova[9] and Srbova.[11]
[c] Sa74-Sa75: Sato et al.[12, 13]
[d] Sampled log uniformly.

Table 3: Exposure scenarios tested for predictions of the quantity of metabolite formed in the bone marrow and the bone marrow exposure to benzene.[a]

Exposure scenario	Continuous background concentration (ppm)[b]	Peak exposure concentration (ppm)[b]	Peak exposure length (min)	TWA benzene exposure (mg/m^3)
Environmental:				
I environmental background[c]	0.0039	-	-	0.0125
II gasoline pumping[d]	0.0036	0.092	15	0.0125
III cigarette smoking[e]	0.00062	0.084	20	0.0132
Occupational:				
IV OSHA PEL	-	1.0	480	0.764
V	-	32.0	15	0.764

[a] Body weight of 70 kg was used for all simulations.
[b] To convert to mg/L multiply by 0.003207, assuming T=25° C and P=1 atm.
[c] Indoor average urban exposure, Wallace et al.[6]
[d] Peak exposures at time 0 and every 5040 minutes thereafter.[7]
[e] Two cigarettes smoked at 6 am., noon, and 6 pm. everyday during the week.[6]

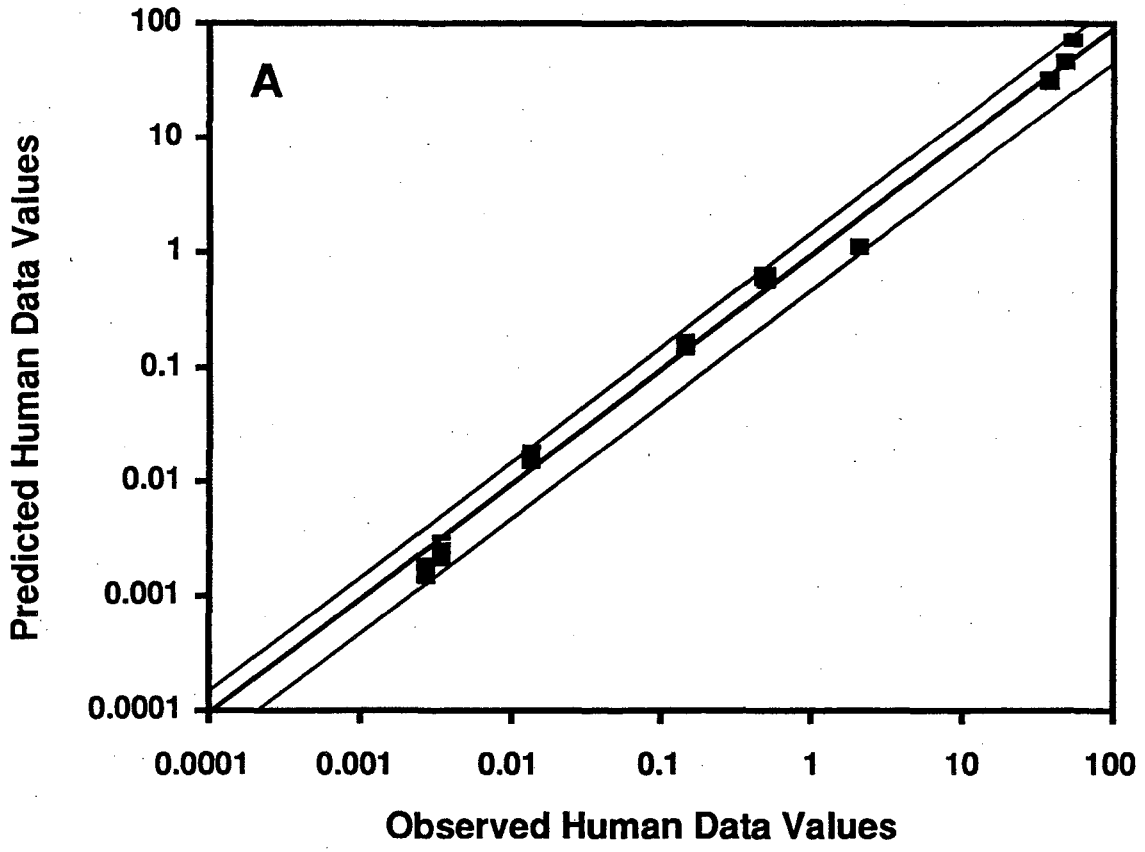
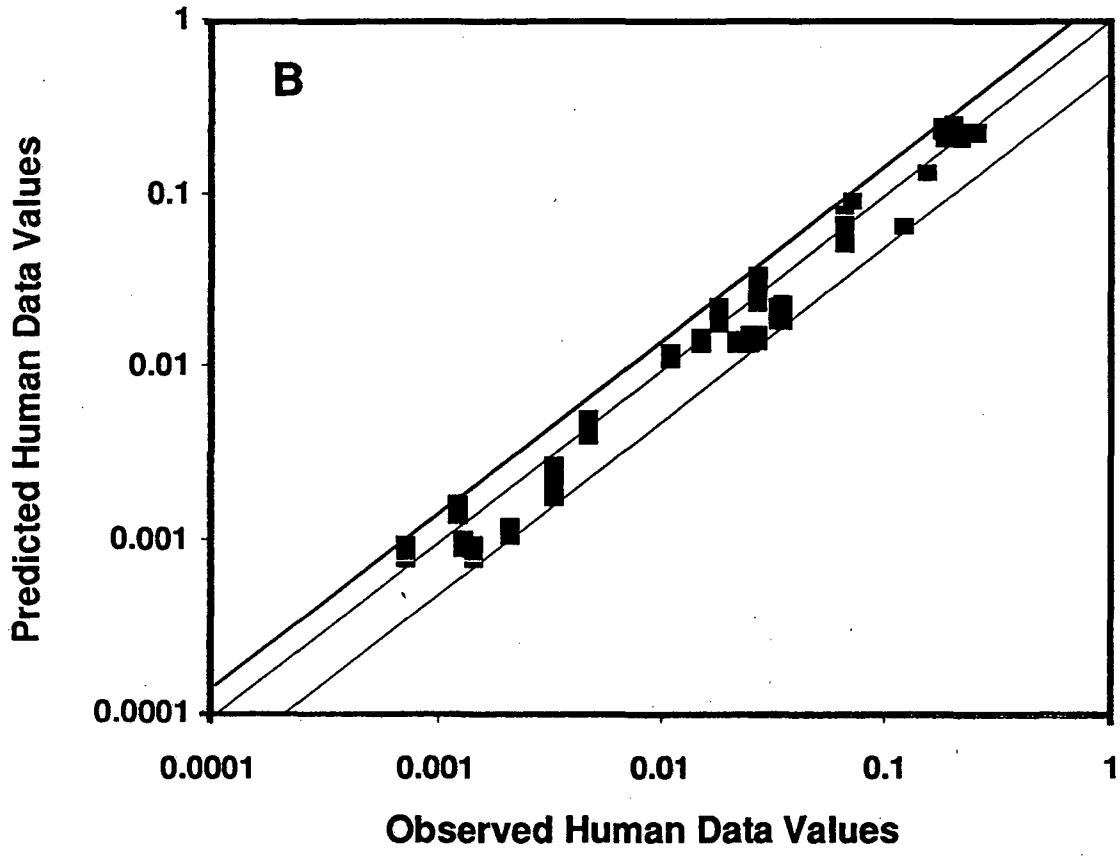


Figure 1: Quality of fit. Model predicted versus observed (experimental) data values. The bounds of ± 50% are indicated by the thin lines. (A) Teisinger and Fiserova-Bergerova[9] and Srbova et al.[11] data. Twenty predictions were made for each of ten observed values. (B) Sato et al.[12, 13] data. Twenty predictions were made for each of twenty-six observed values.



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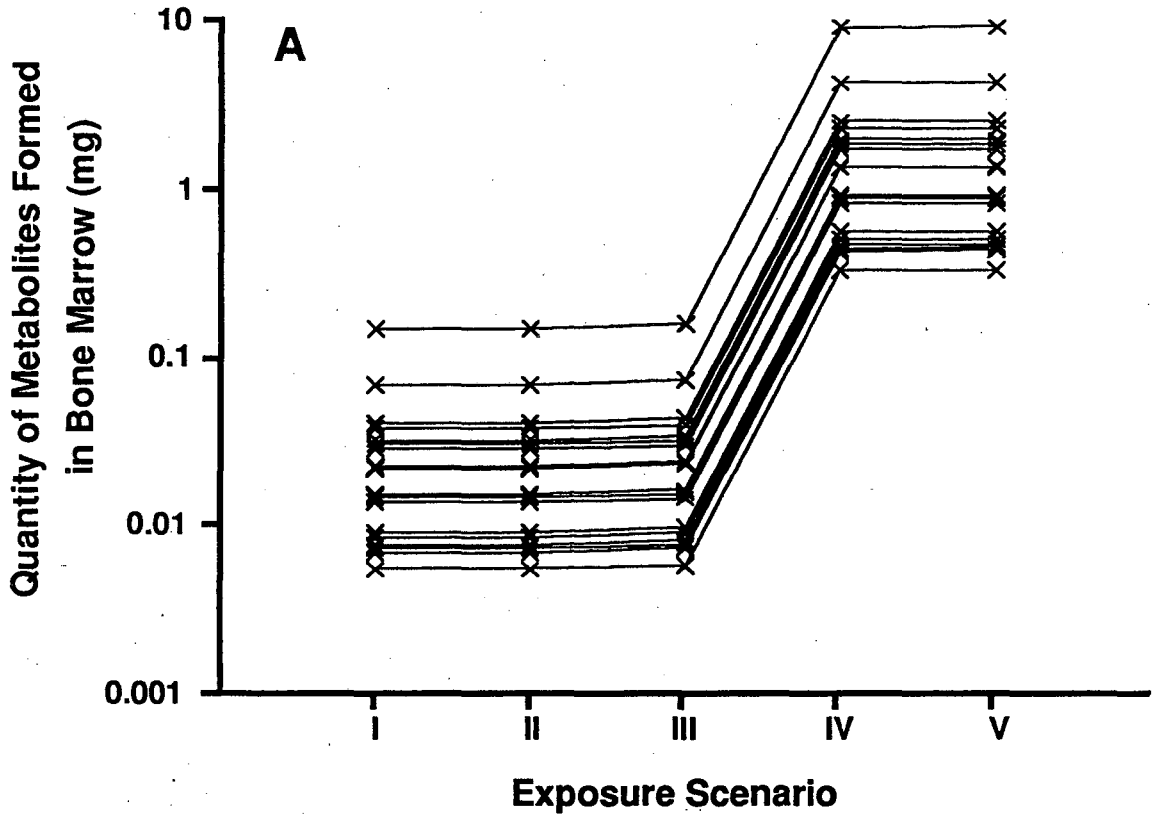
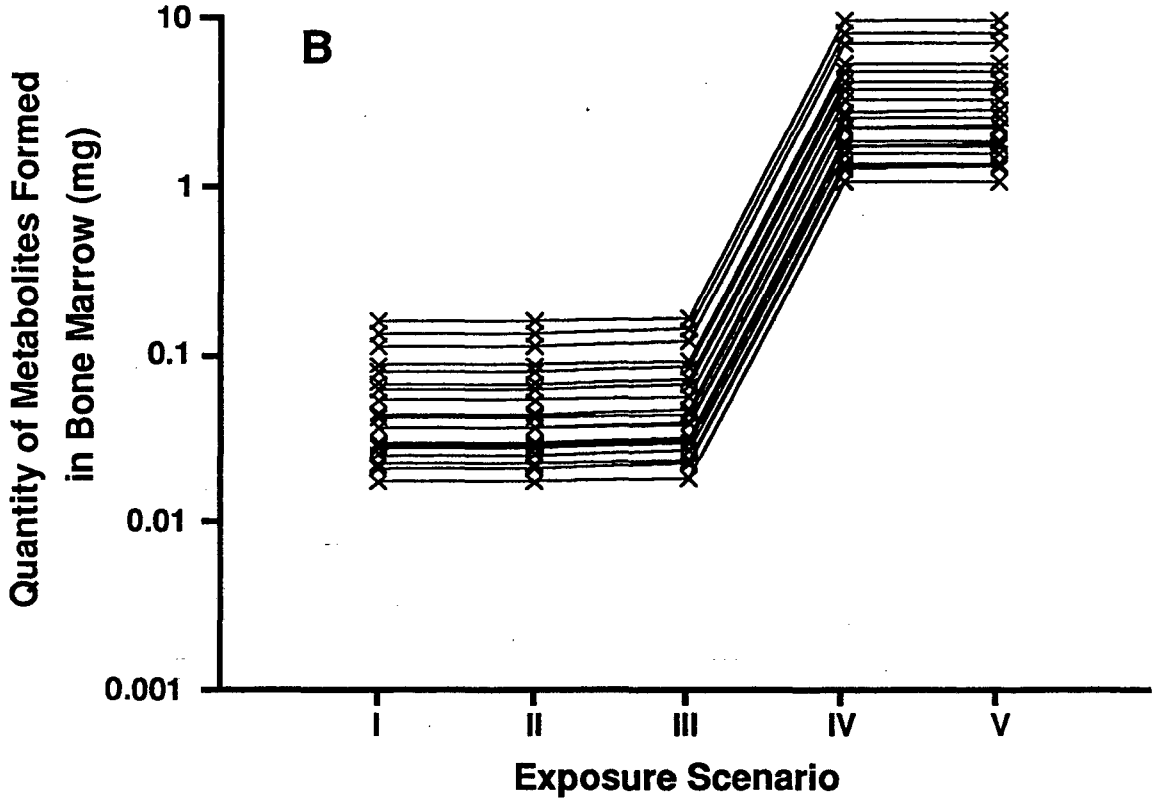


Figure 2: The quantity of metabolite formed in the bone marrow over 1 week at steady-state for environmental exposure scenarios I-III and occupational exposure scenarios IV and V. (A) Model based on Teisinger and Fiserova-Bergerova[9] and Srbova et al.[11] data. (B) Model based on Sato et al.[12, 13] data. Connected markers are the output from each PASS parameter set.



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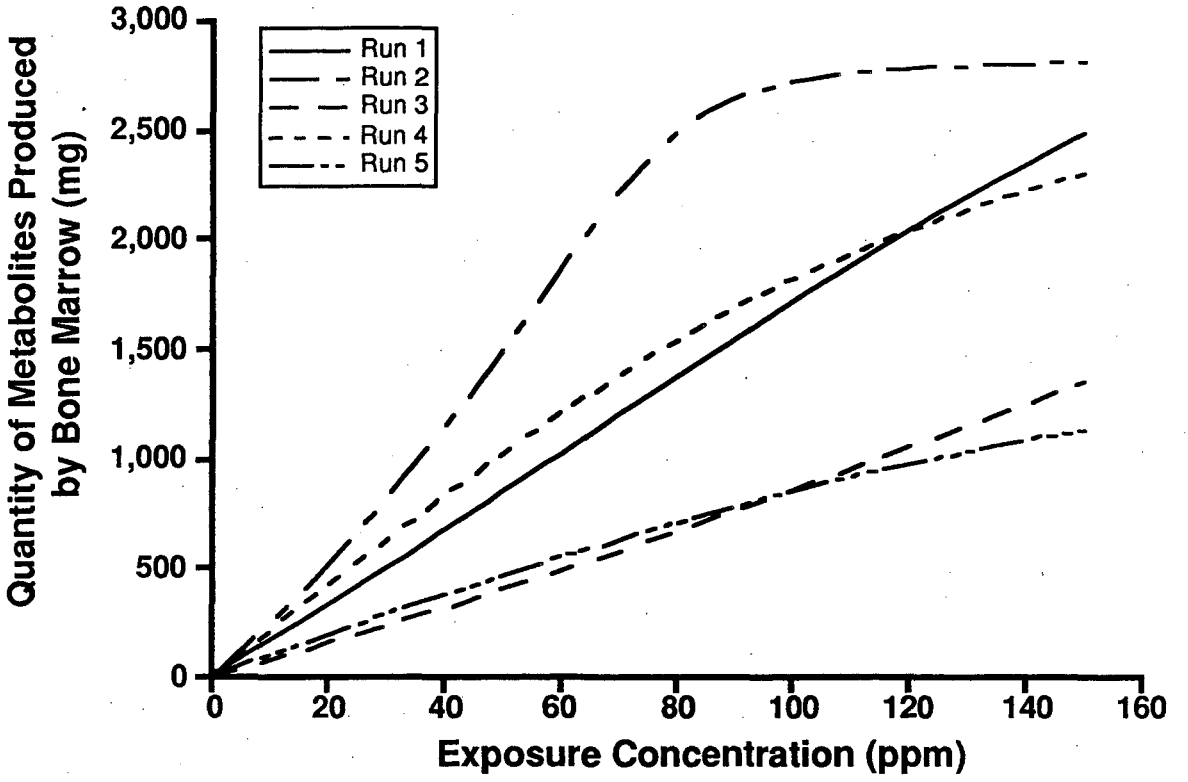

Figure 3: The quantity of metabolite formed in bone marrow over 1 week at steady-state versus the inhalation concentration. First five out of twenty curves obtained by fitting Sa74 and Sa75 data.

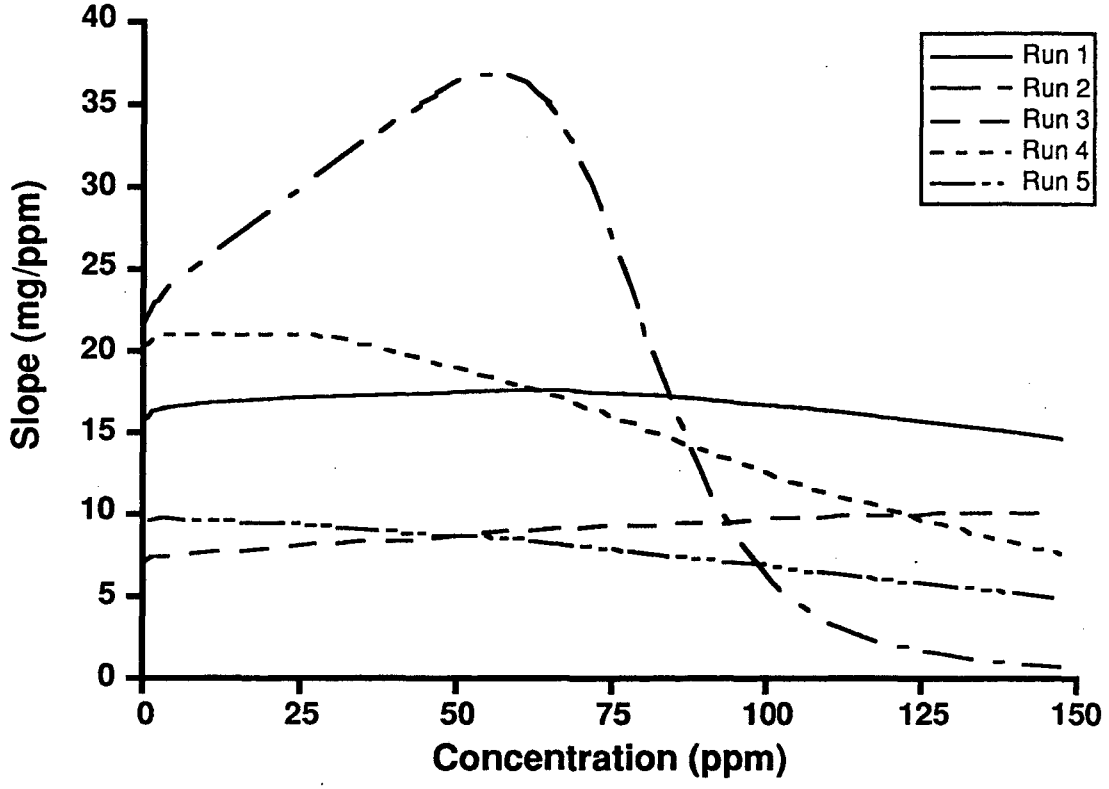

Figure 4: The slope between each pair of adjacent points in Figure 3 versus the mean concentration between these two points.

Appendix: Definition of the criteria used for the human exposure experiments. Predicted concentrations must be within the given ranges for the simulation to be classified as a pass.

Criteria #	Experiment[a]	Type[b]	Time (min)[c]	Exp. Value	Lower Bound (-50%)	Upper Bound (+50%)
1	T	Qph	480.00	2.03	1.02	3.05
2	T	Qph	960.00	36.8	18.4	55.2
3	T	Qph	1200.00	48.4	24.2	72.6
4	T	Qph	2520.00	52.8	26.4	79.1
5	Sr	Cexp	60.00	0.144	0.072	0.216
6	Sr	Cexp	150.00	0.0135	0.00675	0.0203
7	Sr	Cexp	330.00	0.0034	0.0017	0.0051
8	Sr	Cexp	480.00	0.0027	0.00135	0.00405
9	Sr	Cven	82.50	0.482	0.241	0.723
10	Sr	Cven	90.00	0.477	0.239	0.716
11	Sa74	Calv	123.55	0.0146	0.0073	0.0219
12	Sa74	Calv	270.79	0.0012	0.0006	0.0018
13	Sa74	Calv	419.08	0.0007	0.00035	0.00105
14	Sa74	Cven	120.00	0.194	0.0971	0.291
15	Sa74	Cven	242.55	0.0257	0.0129	0.0386
16	Sa74	Cven	303.22	0.0173	0.00865	0.026
17	Sa75m	Calv	132.00	0.0105	0.00525	0.0158
18	Sa75m	Calv	175.00	0.0045	0.00225	0.00675
19	Sa75m	Calv	235.00	0.0032	0.0016	0.0048
20	Sa75m	Calv	385.00	0.00125	0.000625	0.00188
21	Sa75m	Cven	10.00	0.12	0.06	0.18
22	Sa75m	Cven	25.00	0.15	0.075	0.225
23	Sa75m	Cven	85.00	0.25	0.125	0.375
24	Sa75m	Cven	180.00	0.064	0.032	0.096
25	Sa75m	Cven	295.00	0.034	0.017	0.051
26	Sa75m	Cven	415.00	0.024	0.012	0.036
27	Sa75f	Calv	125.00	0.021	0.0105	0.0315
28	Sa75f	Calv	215.00	0.0032	0.0016	0.0048
29	Sa75f	Calv	335.00	0.002	0.001	0.003
30	Sa75f	Calv	425.00	0.0014	0.0007	0.0021
31	Sa75f	Cven	15.00	0.07	0.035	0.105
32	Sa75f	Cven	65.00	0.18	0.09	0.27
33	Sa75f	Cven	95.00	0.175	0.0875	0.263
34	Sa75f	Cven	125.00	0.212	0.106	0.318
35	Sa75f	Cven	305.00	0.0325	0.0163	0.0488
36	Sa75f	Cven	425.00	0.026	0.013	0.039

[a] T = Teisinger and Fiserova-Bergerova,[9] body weight = 70 kg.; Sr = Srbova et al.,[11] body weight = 70 kg.; Sa74 = Sato et al.,[12] body weight = 60 kg.; Sa75m = Sato et al.[13] males, body weight = 60 kg.; and Sa75f = Sato et al.[13] females, body weight = 55 kg.

[b] Calv = concentration of benzene in alveolar air (mg/L), Cexp = concentration of benzene in expired air (mg/L), Cven = concentration of benzene in venous blood (mg/L), Qph = cumulative excreted phenol and its conjugates (mg).

[c] Time from the start of the experiment.

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