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Interspecies Scaling of the Pharmacokinetics of *N*-Nitrosodimethylamine[1]

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ABSTRACT

The pharmacokinetics of *N*-nitrosodimethylamine was studied in patas monkeys following i.v. doses of 0.5, 1.0, and 5.0 mg/kg and a p.o. dose of 1.0 mg/kg, and in Swiss mice at i.v. doses of 1.0 and 2.0 mg/kg. In the patas monkey the pharmacokinetics was linear over the i.v. dose range studied. The mean clearance (Cl), steady-state volume of distribution (V_{ss}), mean residence time, and elimination half-life ($t_{1/2}$) were 103.3 ± 26.7 (SD) ml/min, 3061 ± 821 ml, 30.8 ± 10.8 min, and 21.1 ± 8.5 min, respectively. Assuming that the pharmacokinetics was linear at the p.o. dose used, the p.o. bioavailability of *N*-nitrosodimethylamine in the monkey was 49%. The pharmacokinetics was also linear in mice, and the average Cl, V_{ss}, mean residence time, and $t_{1/2}$ were 3.81 ml/min, 21.0 ml, 5.5 min, and 11.9 min, respectively. These data and data for rats, hamsters, rabbits, dogs, and pigs taken from the literature were used to scale Cl and V_{ss} to body weight using the allometric equation. The resulting equation for Cl was $Cl = 49.7B^{0.998}$ and the equation for V_{ss} was $V_{ss} = 748B^{1.05}$ where B is body weight in kg. The fit of the data to the equation was excellent in both cases. Using these equations and assuming a body weight of 70 kg for humans, the Cl and V_{ss} for *N*-nitrosodimethylamine in humans are estimated to be 3450 ml/min and 64,800 ml, respectively.

INTRODUCTION

Attempts to assess the risk posed to humans by chemical carcinogens are usually based on studies performed in rodents exposed to relatively high doses of the carcinogen for a substantial fraction of their life span (1). The data are then extrapolated to lower doses to which humans may be exposed for an undetermined period of time. The accuracy of this process depends on knowledge and understanding of the ways in which the animal models resemble and differ from the human with regard to the various parameters that determine or modify the effect of carcinogens. These parameters include a wide range of phenomena from disposition and clearance (pharmacokinetics) at the whole animal level to enzymatic activation and macromolecular alterations and repair in the cell.

At the present time, pharmacokinetics is a particularly attractive factor to study in this regard, since it has become increasingly apparent that the qualitative and quantitative impact of a carcinogen may be profoundly altered simply by changing its rate of clearance and pattern of distribution (2–4). This implies that analysis and modulation of the pharmacokinetics of cancer-causing chemicals in the human could contribute in an important way to both risk assessment and risk management.

Can the pharmacokinetics of carcinogens in humans be understood on the basis of extrapolation from animal models? Workers have started to address this question using a representative of an important class of environmental carcinogen, NDMA.[4] Nitrosamines, especially NDMA, occur widely in human exposure sources, form *in situ* by nitrosation and transnitrosation of amines and amides, and are frequently detected in low concentrations in human tissues (5–7). Also there is evidence that alterations in the pharmacokinetics of NDMA by suppression of hepatic metabolism permits or increases tumorigenicity at extrahepatic sites (8–12). Understanding the relevance of such pharmacokinetic phenomena for the human is important, and the data presented here suggest that it may be at least partially attainable by the experiments involving interspecies comparisons.

In our laboratories and those of others, data have been accumulating on the pharmacokinetics of NDMA in the hamster (13), rat (12, 13), rabbit (14), dog (15), and pig (16). In this paper, data for the mouse and patas monkey are added to yield data for a total of seven species ranging widely in size and representing phylogenetically and physiologically disparate organisms. Allometric analysis, a process which correlates a physiological function or condition with body weight, was then undertaken with these data. Several authors have shown for a variety of chemical compounds that pharmacokinetic parameters such as half-life, clearance, intrinsic clearance, and volume of distribution varied simply as a function of body weight (17–24). Thus, in double-log plots, these parameters varied linearly with weight for species ranging in weight from 30 g to 70 kg. The potential for extrapolation to the human was evident when data from a sufficient number of species varying widely in body weight were available.

In performing the same interspecies scaling of pharmacokinetic parameters for NDMA in seven species, a consistent pattern emerged for this compound, with some interesting comparative differences in variation of clearance and bioavailability. The results are potentially extrapolatable to humans and have provocative implications regarding the potential biological effects of this chemical.

MATERIALS AND METHODS

Chemicals. NDMA was obtained from Sigma Chemical Co. (St. Louis, MO). Antifoam B was acquired from Fisher Scientific Co. (King of Prussia, PA). Morpholine (Aldrich Chemical Co., Milwaukee, WI) was double distilled and stored under nitrogen. All other chemicals were ACS reagent grade or better.

Pharmacokinetics of NDMA in Mice. Male Swiss mice [(CR:NIH(s))], 6–8 weeks old with an average weight of 27 g were obtained from the Animal Production Area of the Frederick Cancer Research Facility. The mice were housed under pathogen-free conditions, and hardwood shavings were used as bedding. Conditions included a 12/12-h fluorescent light/dark cycle, the temperature was maintained at 24 ± 2°C, and humidity at 55 ± 5% (SD). The diet consisted of NIH 31 Open Formula

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[4] The abbreviations used are: NDMA, *N*-nitrosodimethylamine; $AUC_{p.o.}$, area under the orally dosed blood concentration *versus* time curve; $AUC_{i.v.}$, area under the i.v. dosed blood concentration *versus* time curve; Cl_s, systemic clearance from blood; Cl_{int}, intrinsic clearance; Q_H, hepatic blood flow; V_{ss}, steady state volume of distribution; F, oral bioavailability; ER, hepatic extraction ratio.

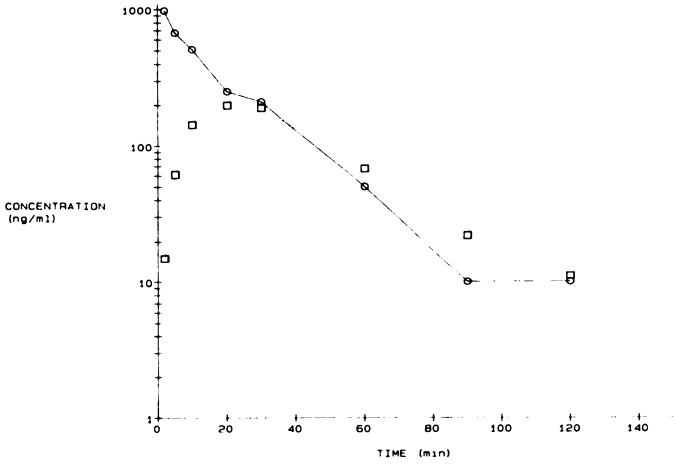

Fig. 1. Typical blood concentration *versus* time profile of NDMA given to monkey R160 at a dose of 1.0 mg/kg both i.v. bolus (○) and orally (□).

Autoclavable Diet and acidified water. NDMA was dosed via the tail vein after warming either the whole animal or just the tail. Pooled blood, 15 mice/time point, was collected in heparinized tubes at specific time intervals by decapitation.

Pharmacokinetics of NDMA in Monkeys. Colony-reared male patas monkeys, weighing 2–4 kg (2–4 years old) were maintained on Purina monkey chow supplemented by fresh fruit and vegetables. Prior to treatment, they were trained to accept restraint and needle insertion without distress, so that treatment could be accomplished without either anesthesia or discomfort to the animal. NDMA was administered via the saphenous vein or by gavage. Blood samples were taken from the femoral vein and placed in heparinized tubes.

Determination of NDMA in Blood. The concentration of NDMA in blood was determined by the method described by Pylypiw *et al.* (25). Briefly, 2 ml of blood, concentrated sulfuric acid, sulfamic acid, and Antifoam B in precise ratios were extracted using methylene chloride with a specially modified extraction-distillation apparatus (11). The samples were then concentrated and analyzed by gas chromatography-thermal energy analyzer. A model TEA-502 thermal energy analyzer (Thermo-Electron Corp., Waltham, MA) was put in series with a HP 5791A packed column gas chromatograph (Avondale, PA).

Pharmacokinetic Calculations. The blood concentration *versus* time data following i.v. dosing were fit to a one or two compartment open model using PHARM, a pharmacokinetic parameter estimation program (26). The goodness-of-fit was determined by visual inspection of both the concentration *versus* time profile and the plot of the residuals. The area under the curve from time zero to the last value was determined using the trapezoidal rule, and the extrapolated area was calculated by dividing the concentration at the final time point by the apparent elimination rate constant. The extrapolated area did not exceed 26% of the total area in any case. The V_{ss}, Cl_s, and mean residence time were determined using noncompartmental methods (27). Bioavailability was determined using Equation A.

$$F = (AUC_{p.o.} * dose_{i.v.})/(AUC_{i.v.} * dose_{p.o.}) \quad (A)$$

Interspecies Extrapolation. With the data obtained in these experiments and those found in the literature, interspecies scaling plots were made. By using the allometric equation

$$y = aB^x \quad (B)$$

where B is body weight and x and a are the allometric exponent and coefficient, respectively, an equation can be obtained in which the body weights of different species can be related to physiological parameters shared by that group. By plotting a specific parameter as a function of body weight on a log-log plot, a line can be fitted to the points with acceptable correlation. The parameters a and x were estimated by performing a weighted ($1/y^2$) nonlinear regression analyses using RS/E (BBN Software, Cambridge, MA).

RESULTS

In the monkey, NDMA concentrations decreased monoexponentially after an i.v. bolus dose (Fig. 1). The AUCs were roughly proportional to the dose which suggests that active processes were not saturated over this dose range (Table 1). Therefore, Cl, V_{ss}, and mean residence time were not dose related and had values of 103.3 ± 26.7 ml/min, 3061 ± 821 ml, and 30.8 ± 10.8 min, respectively. The mean half-life of NDMA in blood was 21.1 ± 8.5 min.

Following a p.o. dose of 1.0 mg/kg, the concentrations of NDMA in blood increased reaching an average C_{max} of 205 ng/ml 25 min after dosing (Fig. 1; Table 2). The concentration then decreased monoexponentially with an average half-life of 22.9 min. Since this half-life is similar to the elimination half-life observed after i.v. administration, it represents an elimination half-life and is not absorption limited. The p.o. bioavailability of NDMA, assuming linear pharmacokinetics, was estimated to be 49%.

In mice, NDMA concentrations decreased biphasically after various i.v. bolus doses (Fig. 2) except in experiment 2 which exhibited a monoexponential decrease in the concentration *versus* time profile. The mice had an average elimination half-life of 11.9 min and a distribution half-life of 3.2 min (Table 3). The average clearance in mice was 3.81 ml/min, and the average V_{ss} was 21.0 ml.

To determine if the pharmacokinetic parameters for NDMA vary predictably with body weight, data from the present study and from the literature were pooled (Table 4) and Cl (Fig. 3)

Table 1 *Pharmacokinetic parameters for NDMA administered i.v. to monkeys*

Patas monkeys were dosed i.v. with 0.5, 1.0, or 5.0 mg/kg NDMA via the saphenous vein. Heparinized blood samples from the femoral vein were analyzed in order to determine the pharmacokinetic parameters.

Animal	Body wt (kg)	AUC (min·ng/ml)	Cl (ml/min)	V_{ss} (ml)	Mean residence time (min)	$t_{1/2}$ (min)
			0.5 mg/kg			
R165	2.34	11,949	97.8	2,242	22.9	15.8
R161	2.60	13,068	100.0	2,954	29.7	20.7
			1.0 mg/kg			
R160	2.68	17,810	149.2	3,322	22.3	14.2
			5.0 mg/kg			
R163	1.80	110,365	81.5	2,464	30.2	19.2
R162	2.95	166,973	88.2	4,322	48.9	35.5
Overall mean ± SD	2.47±0.43		103.3±26.7	3,061±821	30.8±10.8	21.1±8.5

Table 2 *Pharmacokinetic parameters for N-nitrosodimethylamine administered p.o. to monkeys*

Patas monkeys were dosed p.o. by gavage with 1.0 mg/kg NDMA. Bioavailability was calculated using 0.5 mg/kg i.v. data.

Animal	AUC (ng/ml·min)	C_{max} (ng/ml)	t_{max} (min)	$t_{½}$ (min)	Mean residence time (min)	F (%)
R160	9,871	199	20	21.9	42.3	40
R178	14,014	211	30	23.9	51.9	57
Av.	11,943	205	25	22.9	94.2	49

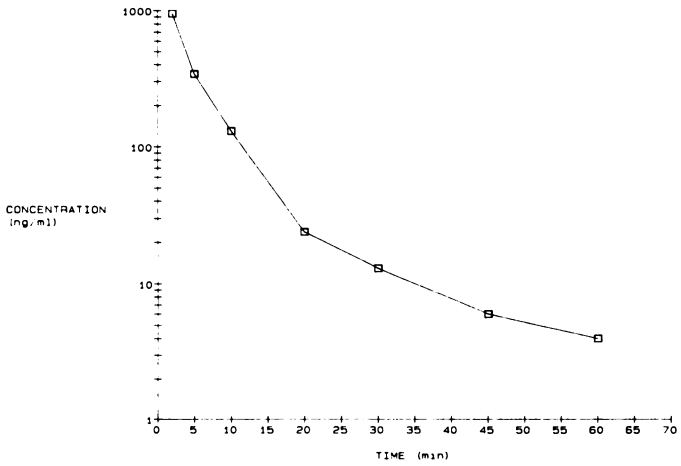

Fig. 2. Typical blood concentration *versus* time profile of NDMA given to mice at 1.0 mg/kg i.v. Individual *points* represent the concentration of pooled samples.

Table 3 *Pharmacokinetic parameters for N-Nitrosodimethylamine administered i.v. to mice*

Male Swiss mice were dosed i.v. via the tail vein with two different doses of NDMA.

Experiment	AUC (ng/ml·min)	Cl (ml/min)	V_{ss} (ml)	Mean residence time (min)	$t_{½}\alpha$ (min)	$t_{½}\beta$ (min)
		1.0 mg/kg				
1	6,773	3.69	24.1	6.5	2.5	15.4
2	7,615	3.28	17.4	5.3	4.1	
		2.0 mg/kg				
3	11,250	4.45	21.5	4.8	3.1	8.3
Mean		3.81	21.0	5.5	3.2	11.9

Table 4 *Pharmacokinetic parameters for NDMA in several animal species*

Species	Body wt (kg)	Q_H[a] (ml/min)	Cl (ml/min)	V_{ss} (ml)	F (%)	Ref.
Mouse	0.025	2.0	3.8	21.0	ND[b]	
Hamster	0.112	7.8	5.6	70.6	11	13
Rat	0.200	13.1	8.0	50.5	8	12, 13
Rabbit	2.5	126	163.0	1,358.0	ND[b]	14
Monkey	2.5	126	103.3	3,061.0	49	
Dog	13.0	549	608.0	22,800.0	93	15
Pig	40.0	1,499	2,516.0	40,000.0	67	16

[a] Hepatic flow rates were calculated from the equation $Q_H = 0.0554B^{0.894}$ (23).
[b] ND, not done.

and V_{ss} (Fig. 4) were fit to the allometric equation. The equations resulting from a nonlinear regression fit are

$$Cl = 49.7(\pm 5.25)B^{0.998(\pm .049)}$$
$$V_{ss} = 748(\pm 116)B^{1.05(\pm .073)}$$

where B is body weight and the allometric parameters are given as the point estimate ± SE.

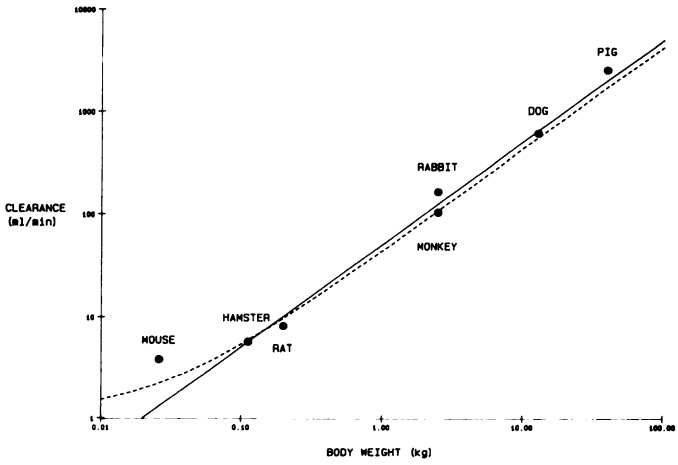

Fig. 3. Interspecies scaling of systemic NDMA clearance as a function of body weight as determined from a weighted ($1/y^2$) nonlinear regression using the allometric equation (——) and from a weighted ($1/y^2$) linear regression (– – – –) presented on a log-log plot. The 95% confidence interval for the allometric equation ($Cl = aB^x$) are $36.2 < a < 63.2$ and $0.872 < x < 1.12$. The 95% confidence interval for the parameters of the linear equation ($Cl = aB + C$) are $24.6 < a < 59.6$ and $-1.03 < C < 3.23$.

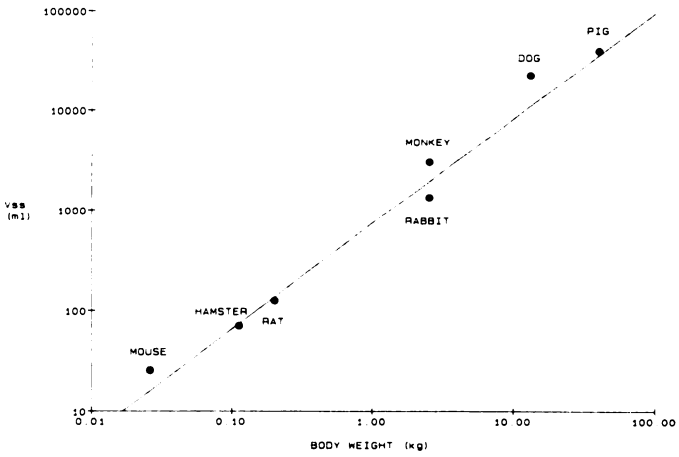

Fig. 4. Interspecies scaling of the steady state volume of distribution of NDMA as a function of body weight. The 95% confidence interval of the parameters from the allometric equation ($V_{ss} = aB^x$) are $450 < a < 1045$ and $0.866 < x < 1.24$.

Since the exponent for clearance was extremely close to 1, a weighted ($1/y^2$) linear regression was performed. The equation obtained from this fit is

$$Cl = 42.1B + 1.10$$

Assuming a body weight of 70 kg for humans, estimates of Cl and V_{ss} for humans from the allometric equation are 3,450 ml/min and 64,800 ml, respectively. An estimate of clearance in humans using the linear equation is 2950 ml/min.

DISCUSSION

The role that the pharmacokinetics of a carcinogen plays in its impact, both qualitatively (*i.e.*, target organ) and quantitatively (*i.e.*, risk assessment), has not been adequately determined for most compounds assumed to be or suspected to be human carcinogens. Data from animals are used to assess the risk based on dose (in mg/kg) without regard for differences in the rate of elimination (clearance) or distribution of the compound between species. It is clear that these factors play a role since, for carcinogens such as the nitrosamines, the route of administration can alter the organospecificity as can manipu-

lation of the clearance with inducers or inhibitors of metabolism. The ultimate question is: what is the pharmacokinetic profile of a given carcinogen in humans? It is obviously unethical to perform an experiment to answer this question, but it may be possible to obtain information that could be useful in estimating the risk to humans without direct measurement in humans. It has been shown for several drugs that key pharmacokinetic parameters such as Cl, Cl_{int}, and V_{ss} can be scaled to body weight using the allometric equation (Equation B) (17–24). An interesting generalization from studies that have been done is that, for compounds cleared primarily by metabolism, the allometric exponent is usually less than 1. That is, larger species tend to have lower clearance than smaller species. This is true of many physiological parameters as well (17). Most active processes tend to be slower in large, long-lived species compared to small, short-lived species. The use of carcinogenicity data obtained in small species (rodents) to estimate risk in larger species (humans), which do not take these differences into account, may introduce an error.

We have attempted this type of analysis with the well-known carcinogen NDMA. It is well established that NDMA must be metabolized to the ultimate methylating species to exert its toxic effect. We collected pharmacokinetic data on NDMA in several species and together with data generated in other laboratories determined the fit of the parameters Cl and V_{ss} to the allometric equation. The fit in both cases was excellent.

An interesting observation, however, was that the allometric exponent for both parameters was close to unity. Therefore the correlations were, in fact, linear; thus risk assessment using an extrapolation based on dose (on a mg/kg basis) appears to be justified for NDMA. Exponents of 1 are expected for the volume of distribution, since V_{ss} is a result of a passive process and total body water scales to a value that is also close to unity (19). However, in many cases, clearance due to metabolism, an active process, scales to an exponent of approximately 0.75 which may reflect a relationship of hepatic blood flow to body weight (22).

In spite of good correlations between body weight and both clearance and V_{ss}, there was not a uniformly predictable relationship between body weight and bioavailability. In general, the smaller species tended to show lower bioavailability than the larger species. If it is assumed that NDMA is cleared solely by hepatic metabolism, bioavailability (F) will ultimately depend on Cl_{int} and hepatic blood flow (Q_H). For a compound that is completely absorbed $F = 1 - ER$ where ER is the hepatic extraction ratio, and $ER = Cl_H/Q_H$, and Cl_H depends upon Cl_{int} and Q_H as shown in Equation C.

$$Cl_H = (Q_H{*}Cl_{int})/(Q_H + Cl_{int}) \quad \text{(C)}$$

If Cl_{int} and Q_H scale differently across species, F will not be a constant function of body weight. In situations where intrinsic clearance greatly exceeds blood flow, then hepatic clearance is blood flow limited and its extraction ratio, and hence bioavailability, should remain constant.

The wide interspecies difference in bioavailability of NDMA is difficult to explain. Compounds with large extractions ratios (>0.8) often show variation in bioavailability on the order of 2-fold, because small changes in ER result in large changes in F. In the case of NDMA, the difference in F between species is about 12-fold despite high clearance in all species. Some other factors that commonly complicate bioavailability determination, including absorption from the gastrointestinal tract and effects due to protein binding and RBC association, do not pertain to NDMA, so an explanation of the anomalous bioavailability data must be sought elsewhere. Most likely, the assumption that the liver is the only clearing organ is incorrect. This interpretation was also supported by the results of an attempt to calculate intrinsic clearance using Equation C.

In all but two cases (rat and monkey), convergence of the iterative process used for solving the equation for Cl_{int} could not be achieved (TK-Solver; Software Arts, Wellesley, MA). For this to occur, the actual hepatic flow rate was lower than that needed to solve the equation; thus, Cl_{int} is blood flow limited and extrahepatic metabolism must occur.

The same conclusion is suggested by the constancy of the systemic clearance per unit body weight among the species, in spite of the apparent wide variation in liver extraction ratios. Possible clearance mechanisms in addition to hepatic metabolism would be excretion of unchanged NDMA in urine or expired in air. Urinary excretion of unchanged compound is minimal, at least in rats, dogs, and monkeys, and, in the monkey, little is found in expired air.[5] With regard to metabolism, kidney has the highest NDMA demethylase activity of the extrahepatic organs, and activity has also been measured in lung (28). If the lung were to play a significant role in the clearance of NDMA then bioavailability estimates may be in error, since extraction of i.v. dose across the lung would reduce the effective dose to the liver and inflate the value of F (Equation A). Recent studies using isolated perfused rat and rabbit lungs have, however, failed to demonstrate any clearance by the lung.[5] In any event, the possibility of significant extrahepatic metabolism in the larger species, with concomitant activation of NDMA to a proximate carcinogen has clear public health implications and is worthy of further study.

Despite the fundamental question of NDMA metabolism raised by these parameters, allometric analyses such as these, should allow estimations of the pharmacokinetic parameters for NDMA in humans. Assuming a body weight of 70 kg for humans, the allometrically extrapolated values of Cl and V_{ss} are 3,450 ml/min and 64,800 ml, respectively. An alternative method for calculating hepatic clearance in humans is to determine enzyme kinetic parameters using human microsomes and extrapolate the data from the enzyme level (*i.e.*, Cl_{int}) to the organ level. This type of analysis by Streeter *et al.* (29) resulted in an intrinsic hepatic clearance of 200 ml/min/kg. This high value for intrinsic hepatic clearance should lead to blood flow limitations in the clearing organ since hepatic blood flow in humans is approximately 20 ml/min/kg. The maximum clearance in humans, assuming no lung clearance, would be approximately 5,000 ml/min (70 ml/min/kg).

We recognize that there are many other processes that play important roles in carcinogenicity that may differ between species, and it is an oversimplification to focus solely on the pharmacokinetics, but to base risk on dose alone is also an oversimplification. If pharmacokinetic data are collected in sufficient number of species covering a wide range of body weight, one can determine if there are any systematic differences in these parameters and perhaps modify risk assessment.

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