

Full Length Research Paper

Extrapolating human toxicity data with target organ dose (TOD- W^b) model: A meso-scale allometric analytical approach

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Received 28 December, 2016; Accepted 24 July, 2017

An allometric target organ dose model (TOD- W^b) with variable scaling exponent, $b = br + bo(bm) - bi$, is proposed for the extrapolation of animal toxicity to human. The exponent b comprises four constituent parameters representing the intake mode to entry organ (bi), route of transportation to target organ (br), mass of target organ (bo), and rate of metabolism at target organ (bm). This expression enables the *a priori* determination of b from known values of bi , br , bo , and bm . From nipradilol that target the respiratory system, the br values determined for intragastric (ig), intraperitoneal (ip), intravenous (iv), and subcutaneous (sc) injections were 0.15, 0.26, 0.03, and 0.61, respectively; from HF mouth breathing data, the br value is 0.07 for pulmonary absorption through inhalation (ih); and from actinomycin D data that target bone marrow through the ip -route, the bo value is 0.53. The model is tested with the parameter values obtained from literature; validating the *a priori* values determined in this paper with the empirical values measured. For ip -administration of OMPA and parathion, the *a priori* $[3/4(bo) - 1]$ value and empirical value are -0.475 and -0.48; for nine alkylating agents, the values are -0.60 and -0.61; for ig -administration of NaCN, the $[br + 3/4(bo) - 1]$ and empirical values are -0.1 and -0.092, respectively. The analysis of toxic gas inhalation data in student projects are also summarized herein. Consequently, values of these parameters can also be estimated by fitting known toxicity data to the TOD- W^b model.

Key words: Target organ dose model, allometric scaling, extrapolating human toxicity.

INTRODUCTION

Dose-response remains fundamental to quantitative assessment of human toxicity. The ability to identify toxicologically equivalent doses for human from different animal species is a challenge and the use of animal toxicity data sets remain essential to interspecies scaling. The two main current approaches to extrapolation of

animal toxicity to human using (1) physiologically based pharmacokinetic (PBPK) model and (2) constant exponent allometric (W^b) model have been well recognized and applied.

The micro-scale PBPK model is knowledge and computation intensive, requiring detailed physiological

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and chemical reaction parameters for computer simulation. This mathematical intensive technique predicts the absorption, distribution, metabolism and excretion of the toxicant through the classical or physiological approach. The classical approach utilizes a lump-compartmental system and fits exponential functions to time-dependent plasma concentration data; while the physiological approach separates the body into a number of interconnected anatomical compartments through the body fluid systems (Gerlowski and Jain, 1983). However, this model is very time-consuming due to large number of parameters; which can be limiting due to parameter identify-ability and redundancy as some of these parameters may be correlated. For the macro-scale constant exponent (W^b) model, there are currently three proponents, each using the allometric scaling according to: (1) body surface area ($W^{2/3}$) or (2) physiological-time ($W^{3/4}$) or (3) body mass (W^1). The use of body surface area criterion has been a long established principle for extrapolating physiological or biological parameters, calculating drug dosages in human; using $b = 2/3$ power rule of the organisms' body weight, a common practice in medical fields (Crawford et al., 1950; Talboy et al., 1953; Prenkel, 1958). This principle was first confirmed empirically with toxicity data of 18 anticancer drugs by Freireich et al. (1966) and evaluated further by Schein et al. (1970). Subsequently, interspecies metabolic rates, cardiac outputs, and ventilation rates were found to have a mass exponent of $3/4$ (Brody, 1945; Kleiber, 1947; Adolph, 1949; Stahl, 1967; McMahan, 1973; Lindstedt and Calder, 1981; Feldman and McMahan, 1983). The support for physiological-time scaling, $b = 3/4$ power rule (Travis and White, 1988) came about after reanalysis of Freireich et al. (1966) and Schein et al. (1970) toxicity data sets and the difference was recognized and attributed to surface area scaling being valid for intraspecies extrapolation; while physiological-time scaling being applicable to interspecies extrapolation. Most recently, publications have revised the support for the body mass scaling, with $b = 1$ power rule; either using the toxicity data in birds (Mineau et al., 1996) and reanalyzing Freireich's data by taking the ratios of toxicity data of difference species with different body mass (Rhombert and Wolff, 1998; Burzala-Kowalczyk and Jongblond, 2011). However, this constant exponent model (W^b) with $b = 2/3, 3/4$ or 1 , does not explain nor reflect the varying exponent values exhibited. It does not take into account the constituent factors when (1) a specific toxicant is administered through different routes of entry and (2) when different chemicals are administered through the same route.

To extrapolate human toxicity data without the PBPK parameter intensity and be able to better explain the constituent factors which the constant exponent (W^b) model did not reflect, an allometric model that incorporates the constituent factors from the route of administration, transport, and the eventual target organ

metabolism of the toxicant would better explain the observed variance. This paper discusses the development of the meso-scale Target Organ Dose allometric scaling model (TOD- W^b), incorporating the constituent factors of (1) intake mode (bi); (2) transport route (br); (3) target organ mass (bo); and (4) target organ metabolism (bm) into the exponent b to enable its *a priori* determination. This target organ dose model (TOD- W^b) will serve as a meso-scale model that lie in between the macro-scale constant exponent (W^b) and the micro-scale PBPK models. The model is also tested with some available toxicity data from literature.

METHODOLOGY

An allometric target organ dose model (TOD- W^b) with variable scaling exponent, $b = br + bo(bm) - bi$, is developed and proposed as a meso-scale model for the extrapolation of animal toxicity to human. The exponent b comprises four constituent parameters representing the intake mode through entry organ (bi), route of transportation to target organ (br), mass of target organ (bo), and rate of metabolism at target organ (bm). This expression enables the *a priori* determination of b from known values of bi, br, bo , and bm .

Fundamentally, when a toxicant is introduced into a species' body, the absorbed amount (internal dose), m_a (mg) is the available dose to be transported to the eventual target organ. This amount is found to be directly proportional to the body weight, W (kg) of the species raised to the mass scaling exponent, b :

$$m_a \propto W^b, \quad (1)$$

When m_a results in 50% lethality, the expression can be written in exposure dose LD_{50} ($k_i W^{bi}$) as:

$$LD_{50} (k_i W^{bi}) \propto W^b, \quad (2)$$

Where, LD_{50} is the median lethal dose. This is the well-recognized and most commonly used allometric scaling rule on the correlation of physiological parameters or biological responses with a nonlinear function of body weight. The expression can be rewritten as:

$$LD_{50} (W^{bi}) = KW^b, \quad (3)$$

Where, K is the overall potency constant (chemical availability and efficacy) associated to the specific toxicant, proportional to its component intake-constant k_i , route-constant k_r , and metabolism-constant k_m as the toxicant travel through its interaction pathway.

Based on the fundamental allometric rule, the effective target organ dose, TOD- W^b is proportional to the mass of toxicant (m) absorbed and transported to the target organ divided by the weight of the target organ, W_o ; raised to the metabolism-exponent, bm at the target organ. Equation 2 can be rewritten as:

$$LD_{50} (W^{bi}) \propto W_o^{bm}, \quad (4)$$

Since the weight of the target organ W_o is proportional to the species' weight W^{bo} , where bo is the exponent for the target organ, the expression can be written as:

$$W_o \propto W^{bo}, \quad (5)$$

and substituting Equation 5 into Equation 4, gives Equation 6

$$LD_{50} (k_i W^{bi}) \propto W^{bo(bm)}, \quad (6)$$

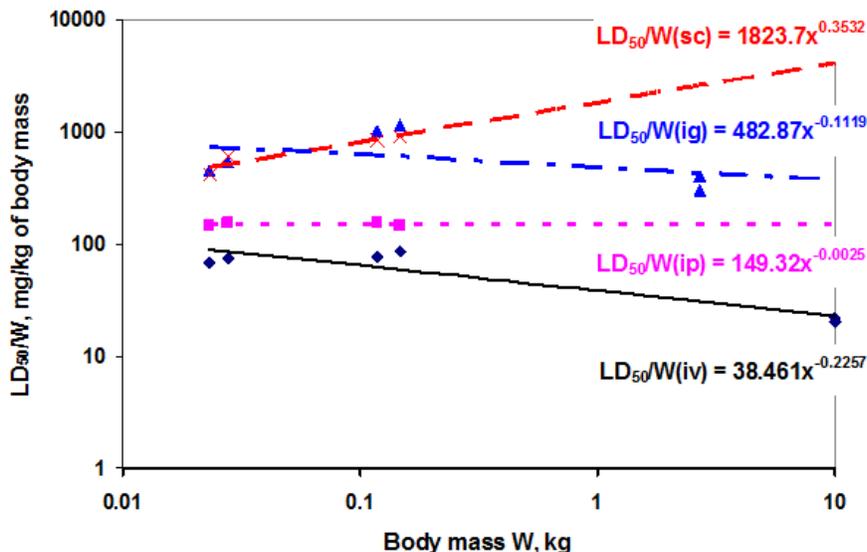


Figure 1. TOD- W^{br} Plot for nipradilol in mammals.

Considering the transport route before the effective dose reaches to the target organ, the effective target organ dose is

$$LD_{50}(k_i W^{bi}) / W^{br} = k_r [k_m W^{bo(bm)}], \tag{7}$$

Rearranging Equation 7 gives the following expressions:

$$LD_{50} (k_i W^{bi}) = k_r k_m W^{br+bo(bm)}, \tag{8}$$

$$LD_{50} = [(k_r k_m) W^{br+bo(bm)}] / (k_i W^{bi}), \tag{9}$$

$$LD_{50} = K W^{br+bo(bm)-bi} \tag{10}$$

Comparing Equations 3 and 10, exponent b can be expressed in its constituent parameters as $br + bo(bm) - bi$; and we believed this expression would better reflect the variance observed as compared to being taken as a mere constant.

RESULTS

To ascertain whether the TOD- W^b model is able to explain the variation observed in the measured values, it is applied to literature toxicity data by comparing the empirical-b values to the *a priori*-b values determined with the model; which uses known values of bi , br , bo , and bm obtained from literature or estimated using toxicity data. Since toxicity data is traditionally reported in mg per kg of body mass, Equation 10 can be expressed as:

$$LD_{50}/W = K W^{br+bo(bm)-bi-1} \tag{11}$$

and using available toxicity data sets, the model can be tested and validated using the following:

(1) Plotting $\text{Log}(LD_{50}/W)$ against $\text{Log}(W)$ for a specific

toxicant administered through various entry-routes to give a series of lines each representing the potency of the toxicant to the target organ with respect to different entry-route and transport-route in relation to the body mass. Using Microsoft Excel, the empirical-b values for each different route of entry and transport can be determined from the respective slopes [slope = $br + bo(bm) - bi - 1$] and compared to the *a priori*-b values determined from the model. Such an analysis is as shown in Figure 1. This is the simplest method and if the number of toxicity data points in each route is small or limited, the accuracy of the analysis can be improved by the use of advanced statistical methodology such as the General Linear Model (GLM). The use of method 2 is recommended.

(2) Plotting $\text{Log}(LD_{50}/W/W^{br})$ against $\text{Log}(W)$ for a specific toxicant administered through various entry-routes with corrected transport-route influence to give a series of parallel lines each representing the potency of the toxicant to the target organ with respect to different entry-route in relation to body mass. Using the GLM methodology, the empirical-b values for each specific entry-route can be determined from the respective slopes [slope = $bo(bm) - bi - 1$] using analysis of covariance (ANCOVA) and compared to *a priori*-b values determined from the model. Such a plot is as shown in Figure 2. For this method, the plot can be cluttered with many lines when the analysis involves a large number of chemicals and routes; in this case, method 3 should be employed to collapse all the lines together into a one-line plot.

(3) Plotting $\text{Log}(LD_{50}/W/W^{br}/K)$ against $\text{Log}(W)$ for a specific toxicant administered through various entry-routes with corrected transport-route influence and potency to give a single line representing the potency of

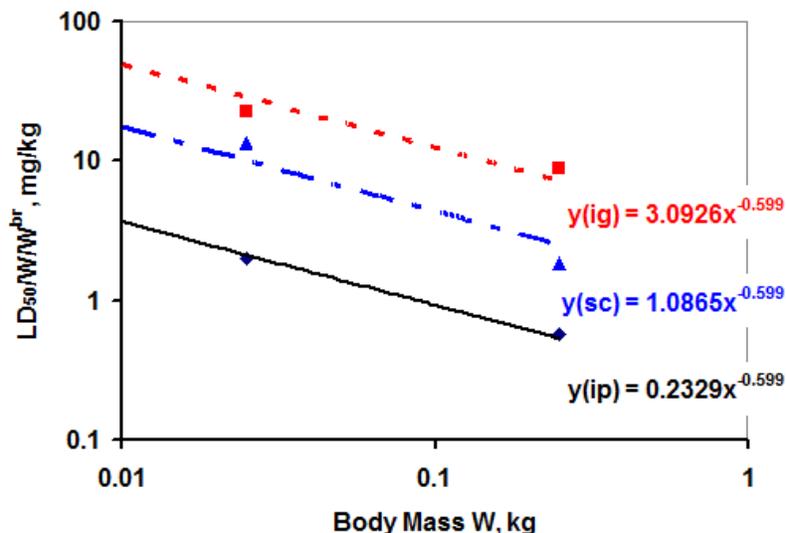


Figure 2. $TOD-W^{br}$ Plot for actinomycin D in mammals.

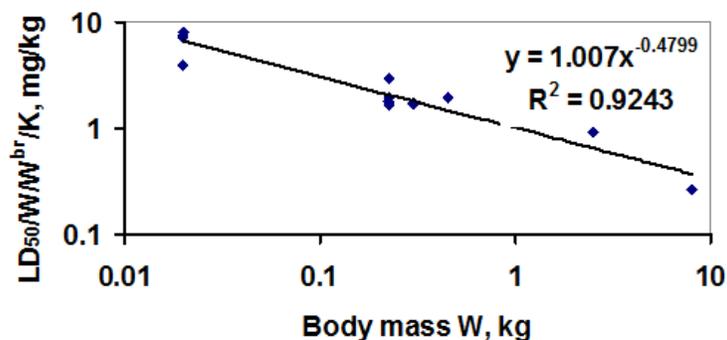


Figure 3. $TOD-W^{br}$ Plot for organophosphates in mammals.

(4) the toxicant to the target organ regardless of entry-routes in relation to body mass. Using Microsoft Excel, the empirical- b values for a specific toxicant can be determined from the common slope [slope = $bo(bm) - bi - 1$] and compared to the *a priori*- b value determined from the model. Such a plot is as shown in Figure 3. This is the preferred and most efficient method to analyze multi-chemicals and multi-routes data sets that has the same target organ.

To test and validate the $TOD-W^b$ model, parameter values for bi , bm , bo , and br are needed. For parameter values that are not found in literature, they are estimated by fitting appropriate toxicity data to the $TOD-W^b$ model.

Constituent parameter values

Generally, two types of dose administration are carried

out in toxicity testing; the forced-intake and *ad libitum* methods. For forced intake (such as intragastric, intramuscular, intraperitoneal, intravenous, or subcutaneous injections), $W^{bi} = 1$ and $bi = 0$ as the full dose of test toxicant is being delivered to the entry site without any losses. The most common forced-intake method is the bolus injection in which a volume of the test toxicant is delivered onto the chosen entry site within a short duration. For *ad libitum* method, the bi values through food intake (Hart et al., 2002) is $2/3$ for birds, 0.72 for mammals and through inhalation (Guyton, 1947a) is $3/4$ for both birds and mammals. And given that $bm = 3/4$ has been well evaluated and accepted for the rate of metabolism (Kleiber, 1947), this value is also adopted for the model.

When the required parameter values are not available, appropriate toxicity data such as that of nipradilol are used to estimate the br values for intravenous (iv), subcutaneous (sc), intragastric (ig), and intraperitoneal

Table 1. Parameter br values for entry-route to target organ.

Entry-route	br Value	Chemical	Source
Intragastric	0.15	Nipradilol	This paper
Intraperitoneal	0.26	Nipradilol	This paper
Intravenous	0.03	Nipradilol	This paper
Subcutaneous	0.61	Nipradilol	This paper
Nasal-larynx	1/3	Aerosol	Guyton, 1947
Pulmonary (alveolus)	0.07	HF, mouth breathing	Lim, 2012

Table 2. Exponent value for organs.

Organ	Mammals	Birds
Brain	0.70 (Brody, 1945; Adolph,1949)	0.50 (Brody, 1945)
Pituitary	0.76 (Brody, 1945; Adolph,1949)	-
Thyroids	0.80 (Brody, 1945; Adolph,1949)	0.86 (Brody, 1945)
Kidney	0.85 (Brody, 1945; Adolph,1949)	0.85 (Brody, 1945)
Liver	0.87 (Brody, 1945; Adolph,1949)	0.88 (Brody, 1945)
Adrenals	0.92 (Brody, 1945; Adolph,1949)	0.89 (Brody, 1945)
Stomach & intestines	0.94 (Brody, 1945; Adolph,1949)	0.92 (Brody, 1945)
Heart	0.98 (Brody, 1945; Adolph,1949)	0.92 (Brody, 1945)
Lungs	0.99 (Brody, 1945; Adolph,1949)	0.94 (Brody, 1945)
Blood	0.99 (Brody, 1945; Adolph,1949)	-
Bone marrow	0.53, this paper	-

(ip) injections, and the actinomycin D toxicity data set is used to determine the bo value for bone marrow.

Analysis of nipradilol toxicity data for br values

Nipradilol toxicity data (Okudo et al., 1985) is analyzed with the TOD-W^b model to determine the br values for intravenous, intraperitoneal, intragastric, and subcutaneous injections by plotting the dosage LD₅₀/W (mg/kg) against the body mass (kg) in a log-log plot (Figure 1). The target organ is reported as the lungs (Okudo et al., 1985) with bo = 0.99 (Brody, 1945; Adolph, 1949); and by setting the exponent value, b = br + (3/4)(0.99) - 1 as the slope of the regression line, the values of br for different entry-routes can be calculated. For example, br for the sc-route is b = br + (3/4)(0.99) - 1 = 0.3532; therefore, the estimated br = 0.3532 + 1 - (3/4)(0.99) = 0.61.

The br values determined in this paper and those from literature are shown in Table 1 as the following.

Analysis of actinomycin D data for bone marrow bo values

Actinomycin D (an alkylating anticancer agent) toxicity data (Phillips et al., 1960) is used to determine the constituent parameter, bo value of bone marrow. The data

set contains LD₅₀/W values for intragastric, intraperitoneal, intravenous, and subcutaneous administration in one single injection. The LD₅₀/W values are adjusted for transport-route influence to LD₅₀/W/W^{br} and plotted against the body mass (kg) in a log-log plot as shown in Figure 2; omitting the iv-route as the data set in this case has only one data point for only one species. By setting the exponent value, b = (3/4)bo - 1 as the slope of the regression line, the bo values of the target organ, regardless of the transport-route, can be calculated. For example, bo for the ig-route is b = (3/4)bo - 1 = -0.599; therefore, the estimated bo = [-0.599 + 1] (4/3) = 0.53.

The bo values determined in this paper and those from literature are shown in Table 2 as the following.

Model testing with toxicity data

The model is tested with toxicity data of two organophosphates in laboratory mammals, sodium cyanide (NaCN) in birds and nine alkylating anticancer agents in mice and rats.

Testing the model with toxicity data of two organophosphates

The toxicity data for OMPA (DuBois et al., 1950) and parathion (DuBois et al., 1949) through the ip-route are

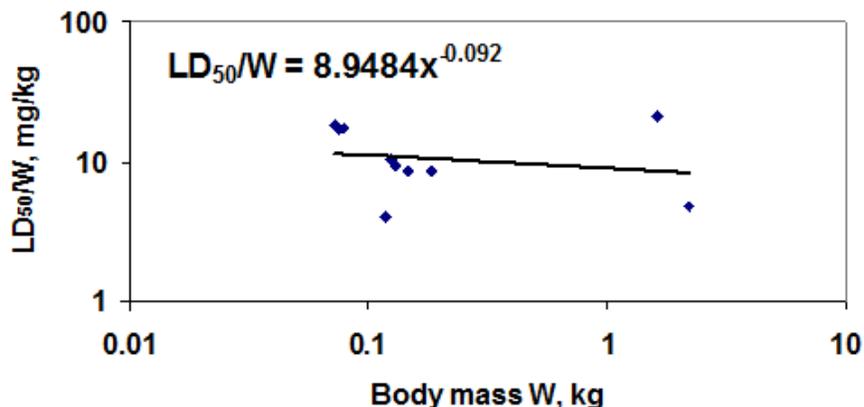


Figure 4. $TOD-W^{br}$ Plot for cyanide in birds.

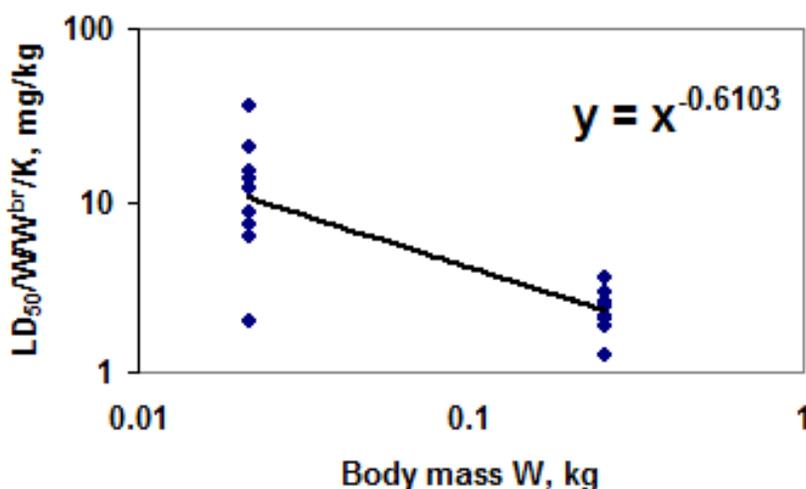


Figure 5. $TOD-W^b$ Plot for nine alkylating agents.

tested against the model together, taking advantage of the same target organ (nervous system) and the structure of the model. The transport-route and potency adjusted variable, $LD_{50}/W/W^{br}/K$ (mg/kg) is plotted against body mass (kg) in a log-log plot (Figure 3). The best fitted line gives the empirical-b of slope -0.480 as compared to the model's slope, *a priori*-b = $3/4bo - 1 = -0.475$ (brain $bo = 0.7$).

Testing the model with toxicity data of sodium cyanide

Testing the model with the toxicity data of oral NaCN in birds (Wiemeyer et al., 1986) gives an empirical-b of -0.092 (Figure 4). With cyanide affecting all cells, $bo = 1$ and oral $ig-br = 0.15$; the model determines the *a priori*-b = $br + (3/4)bo - 1 = -0.1$.

Testing the model with toxicity data of nine alkylating anticancer agents

The toxicity data of nine alkylating agents (Philips and Thiersch, 1950) on mice and rats is used in this analysis. The chemicals were administered by one single ip-injection. The $LD_{50}/W/W^{br}/K$ is plotted against W in a log-log plot (Figure 5) and the slope was obtained by the regression analysis, empirical-b = -0.61. The model's slope, *a priori*-b = $(3/4)bo - 1 = -0.60$ (bone marrow $bo = 0.53$ from actinomycin D toxicity data analyzed in 3.1.2).

Model testing results

In addition to the toxicity data sets used to test and validate the model in this paper, six nerve gas agents, two hydrazines, two mineral acids, three hypoxic gases,

Table 3. Summary of TOD- W^b model testing.

Chemical	bo	Entry route	Empirical slope value	Model expression and <i>a priori</i> slope value	Source
OMPA	0.7	ip	-0.480	$(\frac{3}{4})bo - 1 = -0.475$	This paper
Parathion	0.7	ip	-0.480	$(\frac{3}{4})bo - 1 = -0.475$	This paper
NaCN	1.00	ig	-0.092	$br + (\frac{3}{4})bo - 1 = -0.100$	This paper
Alkylating agents	0.53	ip	-0.61	$(\frac{3}{4})bo - 1 = -0.60$	This paper
HF, nose breathing	0.99	ih	0.28	$br + (\frac{3}{4})bo - \frac{3}{4} = 0.33$	Lim, 2012
HF, mouth breathing	0.99	ih	-0.0076	$(\frac{3}{4})bo - \frac{3}{4} = -0.0075$	Lim, 2012
HCl	0.99	ih	0.33	$br + (\frac{3}{4})bo - \frac{3}{4} = 0.33$	Lim, 2012
Cl ₂	0.99	ih	0.34	$br + (\frac{3}{4})bo - \frac{3}{4} = 0.33$	Xiao, 2012
NH ₃	0.99	ih	0.16	$br + (\frac{3}{4})bo - \frac{3}{4} = 0.20$	Xiao, 2012
MMH	0.85	ih	-0.045	$br + (\frac{3}{4})bo - \frac{3}{4} = -0.043$	Xu, 2012
Nerve gases	0.7	ih	-0.18	$br + (\frac{3}{4})bo - \frac{3}{4} = -0.16$	Tan, 2012
DMH	0.7	ih	-0.084	$br + (\frac{3}{4})bo - \frac{3}{4} = -0.16$	Goh, 2012
H ₂ S, HCN, CO	1.0	ih	0.081	$br + (\frac{3}{4})bo - \frac{3}{4} = 0.07$	Mak, 2012

MMH, Monomethylhydrazine; DMH, Dimethylhadrazine. Ip, intraperitoneal; ig, intragastric; ih, inhalation; iv, intravenous.

and two corrosive gases were analyzed by students; the overall results are summarized subsequently (Table 3).

DISCUSSION

From the test, it was observed that the model *a priori*- b determined is congruous to the empirical- b from the measured toxicity data and is able to fully explain the observed variance when used to analyze toxicity data of systemic and local effects, including chemicals toxic to the respiratory, alkylating agents, hypoxic chemicals, nerve agents, renal toxic chemicals, irritating, and corrosive chemicals.

Studies also showed that the br value appears to be constant for a specific route indicating that there is a base- br value for each entry-route. The actual br value would be higher than the base- br value when there is a chemical-route specific interaction present. This behavior has been observed in some chemical toxicity studies (Sato and Nakajima, 1978; Jadhav et al., 2007). Hence, the current model needs further development to account for the following situations.

The presence of specific chemical-route interaction along the path from the entry-site to the target organ

Any departure from the expected pattern may signal the occurrence of specific chemical-route interaction along the path. Physiological and pathological studies should be carried out to clarify the possible chemical-route behavior in the test system. For examples, nasal deposition may cause local, systemic or direct effects to the brain via the olfactory region that by-passing the

blood-brain barrier or the first-pass effect through the liver in the oral route (Jadhav et al., 2007).

The experimental b values for the iv route involving four chemicals are used to illustrate the differences in the slopes of LD/W against W plots as compared to those obtained from the fixed exponent model (slope = $b - 1$) or from the TOD- W^b model (slope = $br + bm(bo) + bi - 1$). For the iv to gastro-intestine route, the experimental slope values are -0.343 in the LD10 data and -0.347 for the LD50 for epi-doxorubicin; and -0.211 and -0.260 for doxorubicin, respectively (Bertazzoli, 1985) as compared to -0.265 in the TOD- W^b model. For the slope values involving iv to bone marrow, they are -0.533 for SOAz (Nakano et al., 1984) and -0.479 for dolastatin-10 (Mirsalis et al., 1999) as compared to -0.565 in the TOD- W^b model. These slope values in the fixed exponent model are $-1/3$ ($b = 2/3$), $-1/4$ ($b = 3/4$) or 0 ($b = 1$) model. The $2/3$ model appears to fit the epi-doxorubicin data; the $3/4$ model fits the doxorubicin data. The TOD- W^b model explains all the data well.

The involvement of multiple organs in the toxic effects

In this situation, the current single target organ model could not be directly applicable. When multiple target organs are involved, the contribution of the secondary target organs to the overall bo value or the toxicity outcome has to be further modeled.

Future studies would be focused on by further validating the TOD- W^b model and re-analyzing published datasets. It is noteworthy that the same set of anticancer agents toxicity data used to established the $2/3$ rule had also demonstrated the support for the $3/4$ and unity rule

when advanced statistical method was employed. The same data sets s being re-analyze in the hope to explain the variance observed with the TOD- W^b model.

However, it is clear that once the toxicant's target organ is ascertained, through toxicological and pathological investigation, the value of exponent b in the TOD- W^b model can be *a priori* determined from the parameter values b_i , b_m , b_o , and b_r from literature when the mode of application (forced vs. *ad libitum*) and respective entry-route is known. Taking advantage of the model structure, animal-to-human route-to-route and chemical-to-chemical extrapolation can be carried out with the limited measured animal toxicity data. It is believed that the model can also be applied to non-mammal species as well.

The TOD- W^b model is tested with some available toxicity data from literature. So far, the study had indicated that TOD- W^b model is able to explain the constituent factors which the constant exponent (W^b) model is unable to reflect. The ability of TOD- W^b model to explain these constituent factors would enable better understanding of the influence and impact of the toxicant's intake mode (b_i), transport route (b_r), target organ mass (b_o) and target organ metabolism (b_m) without the intensity of PBPK model; serving as a meso-scale model that lie in between the macro-scale constant exponent (W^b) and the micro-scale PBPK models.

Conclusion

From datasets of cancer drugs and anesthetics, and nipradilol that target the respiratory system, the b_r values determined for intragastric (ig), intraperitoneal (ip), intravenous (iv) and subcutaneous (sc) injections are 0.15, 0.26, 0.03, and 0.61, respectively; from HF mouth breathing data, the b_r value is 0.07 for pulmonary absorption through inhalation (ih); and from data of actinomycin D that target bone marrow through the ip-route, the b_o value is 0.53. The model is tested with the parameter values obtained from literature; validating the *a priori* values determined in this paper with the empirical values measured. For ip-administration of OMPA and parathion, the *a priori* [$3/4(b_o) - 1$] value and empirical value are -0.475 and -0.48; for nine alkylating agents, the values are -0.60 and -0.61; for ig-administration of NaCN, the [$b_r + 3/4(b_o) - 1$] and empirical values are -0.1 and -0.092, respectively. The analysis of toxic gas inhalation data in student projects are also summarized herein. Consequently, values of these parameters can also be estimated by fitting known toxicity data to the TOD- W^b model.

Generally, the TOD- W^b model has been tested and validated successfully to toxicity data of a single chemical administered through different routes as well as group of chemicals of the same family having the same target organ, including a set of bird toxicity data. It was believed that this TOD- W^b model is an improvement over the

traditional constant exponent model as it agrees better with measured toxicity data and requires less computation resources as compared to the micro-scale PBPK model. The variable exponent, $b = b_r + (b_o)(b_m) - b_i$, takes into account the influence of the intake-mode (b_i), transport-route (b_r), target organ mass (b_o), and the metabolism at the target organ (b_m).

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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