QSAR METHOD REPORTING FORMAT

QMRF FOR 1Co-PBK RAT MODEL IN BET

CONTENTS

TABLES

FIGURES

1 QSAR IDENTIFIER

1.1 QSAR identifier

One Compartment Physiologically-based Biokinetic (1Co-PBK) mass balance model for a representative laboratory rat in the Bioaccumulation Estimation Tool (BET) available in the Exposure And Safety Estimation (EAS-E) Suite on-line platform (www.eas-e-suite.com). **This model is not a QSAR; however, the QMRF provides some pertinent information regarding the model.**

1.2 QSAR related models

A version of this 1Co-PBK mass balance model is also coded in the Bioaccumulation Assessment Tool (BAT) available for download at https://arnotresearch.com/bat/.

1.3 Software coding

BET v1.0 in Exposure And Safety Estimation (EAS-E) Suite (Ver.0.98 - BETA, release April, 2025). www.eas-e-suite.com.

2 GENERAL INFORMATION

2.1 Date of QMRF

April 2025

2.2 QMRF authors and contact details

Jon Arnot, PhD (jon@arnotresearch.com) and Alessandro Sangion, PhD (alessandro@arnotresearch.com)

2.3 Date of QMRF updates

Not applicable

2.4 QMRF updates

Not applicable

2.5 Model developer and contact details

Jon Arnot is the President of ARC Arnot Research and Consulting Inc. (ARC) and is the primary point of contact for the model and this QMRF: jon@arnotresearch.com. The 1Co-PBK mass balance model for a rat in the Bioaccumulation Estimation Tool (BET) was developed in collaboration between Drs. Jon Arnot (ARC), James Armitage (ARC), Alessandro Sangion (ARC), Trevor Brown (ARC), and Ms Liisa Toose (ARC).

2.6 Date of model development and/or publication

Arnot JA, Toose L, Armitage JM, Embry M, Sangion A, Hughes L. 2023. A weight of evidence approach for bioaccumulation assessment. Integrated Environmental Assessment and Management 19:1235–1253. DOI: 10.1002/ieam.4583.

2.7 References to main scientific papers and/or software package

ARC Arnot Research and Consulting. **2025**. Bioaccumulation Estimation Tool (BET) in the Exposure And Safety Estimation (EAS-E) Suite. Available from: www.eas-e-suite.com

Arnot JA, Toose L, Armitage JM, Embry M, Sangion A, Hughes L. **2023**. A weight of evidence approach for bioaccumulation assessment. Integrated Environmental Assessment and Management 19:1235–1253. DOI: 10.1002/ieam.4583.

2.8 Availability of information about the model

Bioaccumulation Estimation Tool (BET) in the Exposure And Safety Estimation (EAS-E) Suite. Available from: www.eas-e-suite.com

2.9 Availability of another QMRF for exactly the same model

A search of the (Q)SAR Model Reporting Format Inventory for ‘BET’ returned no results.

3 DEFINING THE ENDPOINT: OECD PRINCIPLE 1

3.1 Species

Rat Genera

3.2 Endpoints and units

BMF (kg-ww/kg-ww; Diet): biomagnification factor calculated on the wet weight chemical concentrations of the consumer and its diet.

BMF_L (kg-lw/kg-lw; Diet): biomagnification factor calculated on the chemical concentrations in the total lipids (adipose and membrane lipid) of the consumer and its diet.

BMF_A (activity/activity; Diet): biomagnification factor calculated on a chemical activity (or fugacity for neutral chemicals) basis. These values are temperature dependent. Temperature correction in EAS-E Suite relies on the enthalpies of phase change. Assumed default enthalpies of phase change are provided in the chemical information tab; however, the use of chemical specific values is recommended.

Total (terminal) Elimination Half-Life (HL_T; hours)

3.3 Comment on the endpoints

The biomagnification factor (BMF) determines whether the chemical activity in an organism is greater than, equal to, or lower than the chemical activity in its diet (generally considers food only) or total ingesta (food and water combined). The Organization for Economic Cooperation and Development (OECD) provides technical guidance for measuring a BMF in fish [1]. A Discussion Paper published by the European Chemicals Agency (ECHA) [2] outlines theoretical background and equations for determining the BMF in air-breathing organisms. Briefly, the BMF can be measured as the ratio of the chemical concentration in an organism (Corg; µg-chemical/kg-rat) and its diet (Cdiet; µg-chemical/kg-diet) as Corg/Cdiet, if steady-state conditions are approximated [1]. Alternatively, the BMF can be calculated kinetically as the ratio of the chemical intake rate constant from diet (k_D; kg-diet/kg-org/d) and the total (terminal) elimination rate constant of the chemical from the organism (k_T; 1/d) as $k_D \times E_D / k_T$, where E_D is the chemical dietary uptake efficiency [1].

The BMF can be expressed in various units. It is generally recommended that for hydrophobic neutral organic chemicals (HNOCs) that the BMF be expressed in lipid-normalized concentration or fugacity ratios. It is generally recommended that for ionizable organic chemicals (IOCs) that the BMF be expressed as chemical activity ratios [2]. Traditionally, the BMF relates the chemical concentration (activity) in an organism to the exposure to that chemical in its diet. In a laboratory experiment the exposure routes can be controlled so that an organism is only exposed to a chemical in its diet. In the environment, organisms are exposed to chemicals from total ingesta (food and water) and from the respiratory medium in which the organism resides, i.e., air for air-breathing organisms. It is noted that laboratory BMFs and field BMFs are thus fundamentally different. In the environment chemical exposure in water may be a significant source of exposure to IOCs.

The total (terminal) elimination half-life (HL_T; hours) is the time required for the chemical concentration in an organism to decrease by 50% when it is no longer exposed to the chemical. The parameter is a function of body mass (kg). All else being equal, larger organisms have a longer HL_T than smaller organisms. For very persistent HNOCs HL_T is also a function of the organism's lipid content (higher lipid contents result in longer HL_T).

3.4 Endpoint units

See 3.2

3.5 Dependent variables

The 1Co-PBK mass balance model for calculating bioaccumulation assessment parameters in a representative laboratory rat as coded in the BET is dependent on (i) physiological parameters of the rat (e.g., body mass, lipid content, protein content), (ii) properties of its diet (e.g., lipid content), (iii) physicochemical properties or biopartitioning properties, and (iv) whole-body primary biotransformation rate constants (k_B; /hour). First-order kinetics are common and often assumed, particularly when the chemical concentration is below the Michaelis-Menten constant (k_{MM}). The whole-body biotransformation rate constant is assumed to be first-order and therefore the corresponding whole-body biotransformation half-life (HL_B) is $HL_B = \ln 2/k_B$. The physiological and dietary parameters are representative of typical experimental conditions for body mass, lipid content, temperature, feeding and drinking rates, and food composition, e.g., "rat chow". These parameters are fixed state variables in the BET.

The EAS-E Suite platform that hosts the BET includes databases and models for chemical-specific parameters required to run the BET, e.g., K_{OW}, K_{OA}, and HL_B, including *in vivo* HL_B data for humans and rodents and *in vitro* biotransformation rate databases based on hepatocyte, S9, and microsomal bioassays from humans and rodent species. SMILES notations can be entered to obtain model predictions for K_{OW} and K_{OA} and HL_B input parameters if experimental values are not available. Users of the BET in EAS-E Suite have options to enter preferred values for partitioning, i.e., K_{OW} and K_{OA}, pka, or biopartitioning or *in vitro*, *in vivo* or *in silico* estimates for biotransformation rates.

3.6 Experimental protocol

There are no standardized test guidelines for measuring a BMF in a laboratory rat; however, HL_T (or total clearance or total elimination rate constants) are TK parameters that can be determined in OECD 417 guidance [3]. The merits and limitations of refining existing OECD test guidelines to develop an explicit lab rat BMF standardized test guideline have been discussed [2, 4].

3.7 Endpoint data quality

Because there are no explicitly measured BMF data from laboratory experiments using rats or standardized BMF test guidelines in rats it is difficult to determine BMF and HL_T data quality. Arnot and colleagues developed some Data Evaluation Templates (DETs) for considering lab rat TK data and those data quality assessment criteria were derived from the OECD 417 TGs [5]. These DETs have been applied to critically evaluate and score approximately 540 measured HL_Ts in rodent species and these data are in EAS-E Suite. It is noted that one of the primary sources of uncertainty in available measured HL_T data is that many studies calculate TK parameters using radiolabelled test chemical and analytical

quantification of concentrations in rat tissues is often based on total radioactive residue (TRR) and not chemical specific analysis. In instances in which parent chemical analysis was not conducted there is uncertainty in the reported TK parameters because TRR can represent the parent chemical and metabolites, i.e. a mixture.

#	Quality Criterion/Consideration	Maximum Score
1	Was the parent/metabolite reported?	5
2	Sample size reported?	10
3	Number of sampling time points reported?	10
4	Chemical purity of the administered compound reported?	5
5	Clarity of reported rate units	10
6	Relevant biological information reported? e.g., strain/sex/age	5
7	Body weight/mass reported?	5
8	Dose reported with units?	10
9	Route of administration reported?	5
10	Test duration reported?	5
11	Dosing reported?	5
12	Frequency of dosing reported?	5
13	Testing of which tissue reported?	5
14	Vehicle used reported?	5
15	Was there a control group?	5
16	Was there an indication of toxicity?	10
17	Was there a toxicokinetic model presented?	5
18	How was the rate of elimination (k_T) / half life (HL_T) determined?	10
20	Critical Fail for other reason (override; quality score = 0)	Fail

Figure 3.1 Criteria for assessing in vivo laboratory TK data quality for mammals, i.e., BMFs and HL_Ts [5].

4 DEFINING THE ALGORITHM: OECD PRINCIPLE 2

4.1 Type of model

The 1Co-PBK model for a rat in the Bioaccumulation Estimation Tool (BET) is a ***mass balance model*** formulated to calculate BMFs (various units) and HL_T (h). The 1Co-PBK modeling approach is generally consistent with other models used to estimate chemical uptake and elimination processes in mammals [5-8], except where noted. All tissues/organs are grouped into a single compartment. While there can be explicit consideration for absorption efficiencies at each portal of entry (e.g., lung, skin, gastro-intestinal tract) there is no explicit and initial consideration for chemical distribution in the organism; the chemical is instantaneously well-mixed throughout the body. Whole-body level data are used for B assessment [1]. The composition of the whole body is however still characterized in terms of key biological phases (e.g., adipose, phospholipids, proteins, water) that can be estimated from the volumes and compositions of individual tissues and is therefore broadly consistent with some multi-compartment PBK mass balance models [9].

4.2 Explicit algorithm

The biomagnification factor (BMF) = k_D / (k_{RO} + k_E + k_R + k_B + k_G)

where k_D is the dietary clearance rate constant kg(kg·h)$^{-1}$ that includes a chemical uptake efficiency from the diet (E_D). The rate constants (h^{-1}) corresponding to chemical elimination via respiratory elimination, fecal egestion, renal excretion, biotransformation, and growth dilution are k_{RO}, k_E, k_R, k_B, k_G, respectively. Growth dilution is a "pseudo" elimination process in that the chemical is not actually eliminated from the organism, but the change in chemical concentration is a function of changes in biomass and is only relevant for highly persistent chemicals. The total first order chemical elimination process is the sum of various individual elimination processes, i.e., $k_T = k_{RO} + k_E + k_R + k_B + k_G$. The rate constants are described below, and **Table 4.1** summarizes the representative physiological parameters for an adult laboratory rat.

The total (terminal) elimination half-life (HL_T) = ln2/k_T

Respiratory Uptake - k_{RI}

In the current model applications for simulating laboratory BMFs, there is no exposure to chemical in the air; however, this equation is required for calculating respiratory elimination, as per below. The respiration intake rate constant k_{RI} is calculated as:

$k_{RI} = E_A G_R / M_R$

where E_A is the chemical transfer efficiency in the lung (unitless), G_R is the respiration rate (L/h), and M_R is the mass of the rat (kg). The estimated alveolar respiration rate is 70% of the total respiration rate and thus E_A is approximated as 0.7 [10, 11].

Respiratory Elimination - k_{RO}

The respiratory elimination rate constant k_{RO} (h^{-1}) is calculated as:

$k_{RO} = k_{RI} / K_{HA}$

where k_{RI} is the respiration intake rate constant (L-air/kg-rat/h) and K_{HA} is the rat-air partition coefficient (kg-rat/L-air) estimated as:

$K_{HA} = (SL_R K_{OA}/\delta_L + PL_R K_{OA}/\delta_L + P_R \rho K_{OA} + SA_R K_{SaA}/\delta_{Sa} + W_R/K_{AW})$

SL_R is the storage (adipose) lipid mass fraction of the rat on a wet weight basis, PL_R is the phospholipid (membrane) mass fraction of the rat on a wet weight basis, P_R is the structural protein mass fraction of the rat on a wet weight basis, SA_R is the serum albumin mass fraction of the rat on a whole body wet weight basis, W_R is the water fraction of the rat, δ_L is the density of lipid and δ_{Sa} is the density of serum albumin. ρ is the proportionality constant expressing the storage capacity of protein to that of octanol [7, 12]. Following this approach the octanol-air (K_{OA}) and air-water (K_{AW}) partition coefficients (dimensionless) for the chemical are used. The serum albumin-air partition coefficient (K_{SaA}) is calculated as the ratio of the serum albumin-water partition coefficient (K_{SaW}) divided by K_{AW}, where K_{SaW} is estimated from octanol-water partitioning using the relationships suggested by Endo and Goss [13].

For ionogenic organic chemicals (IOCs) that are ionized at pH 7.4 K_{OA} and K_{AW} are replaced by the chemical-specific distribution coefficients D_{OA} and D_{AW}, respectively and K_{SaA} is replaced by a distribution ratio (D_{SaA}). Distribution ratios for IOCs are determined using the Hendersen-Hasselbalch equation and scaling factors relating the partitioning of the charged form of the chemicals to those of the neutral form, e.g., [9]. In the BET, if biopartitioning data are available, e.g., storage lipid-water partition or distribution ratios, $K_{SL\text{-}W}$ or $D_{SL\text{-}W}$, they can be used as model input parameters directly circumventing the use of octanol as a surrogate for biological component partitioning.

Ingestion Uptake - k_D

The ingestion intake rate constant k_D (kg-ingested(kg-rat·h)$^{-1}$ is calculated as:

$k_D = E_D G_D / M_R$

where E_D is the chemical transfer efficiency from the gastrointestinal tract GIT (unitless), G_D is the ingestion rate (kg/h) and M_R is the rat mass (kg). Chemical uptake efficiency is based on a GIT residence time model developed by Arnot and Mackay [14] which has been parameterized here for mammals. **Table 4.2** summarizes the E_D parameters for mammals. The 1Co-PBK model includes a digestion model that simulates chemical biomagnification from the GIT into the body. This mechanistic biomagnification model is well-established [6, 7, 15-17] and explicitly considers the degree to which ingested materials are digested in the GIT and subsequently assimilated into the body, which along with the composition of the body, determines the fugacity (chemical activity) gradient (i.e., the driving force for passive diffusion of chemical into the body).

Fecal Egestion - k_E

The fecal egestion rate constant k_E (h^{-1}) is:

$k_E = G_F E_D K_{GH} / M_R$

where G_F (kg-ww/h) is the fecal egestion rate, K_{GH} is the partition coefficient of the chemical between the GIT and the rat (kg-rat/kg-feces), and E_D (unitless) is the chemical transfer efficiency between the

GIT and the rat. G_F was calculated from the feeding rate G_D (kg-food/h), the digestibility of the diet, and the composition of the diet as:

$$G_F = ([(1-\varepsilon_L)L_D + (1-\varepsilon_P)P_D + (1-\varepsilon_C)C_D + (1-\varepsilon_W)W_D]G_D)/(L_G + P_G + C_G + W_G)$$

where ε_L, ε_P, ε_C and ε_W are the dietary absorption efficiencies of lipid, protein, carbohydrate, and water, respectively. L_G, P_G, C_G and W_G are the mass fractions (kg/kg) in the gut (feces) calculated below.

The degree to which ingested nutrients are absorbed and assimilated by the body influences the degree to which chemicals are subsequently absorbed as reflected by K_{GH}. For neutral organics K_{GH} is calculated as:

$$K_{GH} = (L_G K_{OW}/\delta_L + P_G \rho K_{OW} + C_G \rho K_{OW} + W_G) / (L_R K_{OW}/\delta_L + P_R \rho K_{OW} + W_R)$$

where L_G, P_G, C_G, and W_G are the lipid, protein and carbohydrate, and water contents of the GIT, respectively, after digestion. For IOCs, K_{OW} is replaced D_{OW}. For simplicity in these equations fats and phospholipids are lumped together as "total lipids" L. The sum of these fractions approach 1 and are dependent on the absorption efficiency for each component of the diet as:

$$L_G = [(1-\varepsilon_L)L_D] / [(1-\varepsilon_L)L_D + (1-\varepsilon_P)P_D + (1-\varepsilon_C)C_D + (1-\varepsilon_W)W_D]$$

$$P_G = [(1-\varepsilon_P)P_D] / [(1-\varepsilon_L)L_D + (1-\varepsilon_P)P_D + (1-\varepsilon_C)C_D + (1-\varepsilon_W)W_D]$$

$$C_G = [(1-\varepsilon_C)C_D] / [(1-\varepsilon_L)L_D + (1-\varepsilon_P)P_D + (1-\varepsilon_C)C_D + (1-\varepsilon_W)W_D]$$

$$W_G = [(1-\varepsilon_C)W_D] / [(1-\varepsilon_L)L_D + (1-\varepsilon_P)P_D + (1-\varepsilon_C)C_D + (1-\varepsilon_W)W_D]$$

Generic estimation of partitioning behaviour of IOCs is based on the behaviour of the neutral form and application of scaling factors for the charged form [12, 18].

Renal Clearance - k_R

The rat 1Co-PBK model in the BET can consider two different sub-modules (models) for renal (urinary) elimination rate constant k_R (h^{-1}). The two basic approaches are equilibrium partitioning approach and the glomerular filtration rate approach as summarized elsewhere [9].

Growth dilution - k_G

Growth dilution is considered a loss process, although parent chemical is not actually eliminated because of this process, rather the chemical concentration can become reduced in the increased mass and volume of the organism as it grows over time. A growth rate constant k_G (h^{-1}) of 6.25×10^{-5} [19] is included to account for some biological turnover and to include some dermal losses (desquamation) and this loss process is only relevant for very persistent chemicals.

Biotransformation – k_B

The biotransformation rates are assumed to follow first-order kinetics. First-order biotransformation rate constants (k_B, h^{-1}) result in a constant fraction of the mass of parent chemical being degraded per unit time. The k_B or whole-body biotransformation half-lives ($HL_B = \ln 2/k_B$) are model input parameters

that can be obtained from various *in vitro* and *in vitro-in vivo* extrapolation (IVIVE) methods, *in vivo* data (when available) or from *in silico* models [5]. In the BET in EAS-E Suite the 1Co-PBK rat model can be parameterized with *in vivo*, *in vitro* or *in silico* data for estimating k_B. In absence of any data the model assumes $k_B = 0$ (no biotransformation). By default, available *in vivo* data from mammals in the built-in EAS-E Suite databases are used to parameterize the model. In absence of *in vivo* data, *in silico* model predictions from built-in HL_B-QSARs are used [20, 21]. If *in vitro* biotransformation rate data for rat from S9 or microsomal assays from liver tissues or hepatocyte assays are available, the user can enter these data and the built-in IVIVE models will calculate k_B to parameterize the model.

Table 4.1. Default parameter values for the 1Co-PBK laboratory rat model

Parameter	Value	Notes/Comments
Mass	0.25 kg	
Temperature	37 °C	
Blood pH	7.4	
Urine pH	6.2	
Proximate Composition		
Storage lipid	0.0800	At whole body level
Membrane lipid	0.0098	
Structural protein	0.1998	
Serum albumin	0.0024	
Water	0.7080	
Key Uptake Rates		
Inhalation	0.00756 m^3/h	
Ingestion (Food)	$5.65x10^{-7}$ m^3/h	5.4% of BW per day
Ingestion (Water)	$1.18x10^{-6}$ m^3/h	
Assimilation Efficiencies		
From lungs (E_A)	0.7	
From GIT (E_D)	*Chemical specific*	*f* of hydrophobicity (K_{OW}), see [14]
Proximate Composition of Diet		Commercial rat chow pellets (dry)
Storage lipid	0.04	
Membrane lipid	0.01	Overall composition of ingesta calculated
Protein	0.24	as a function of food and water ingestion
Carbohydrates	0.54	rates
Water	0.17	
Dietary Assimilation Efficiencies		
Storage lipid	0.95	
Membrane lipid	0.95	
Protein	0.75	
Carbohydrates	0.75	
Water	0.85	
Key Elimination Rates		
Exhalation	0.0075 m^3/h	*f* of total ingestion & assimilation
Fecal egestion	-	
Urinary elimination	$1.09x10^{-6}$ m^3/h	
Growth rate constant	$1.55x10^{-8}$ m^3/h	

Table 4.2. The chemical dietary absorption efficiency model [14] and parameters for mammals [5] used in the 1Co-PBK model.

Parameters	Mammals
$E_D = 1 - \exp\left(-\frac{\tau_G}{\tau_A}\right)$	
$\tau_G = \frac{1}{\left(\frac{1}{\tau_{rxn}} + \frac{1}{\tau_{trans}}\right)}$	
$\tau_A = VW + VOct * Kow * \left(\frac{1}{GOct * Kow} + \frac{1}{Gw}\right)$	
GOct	$3x10^{-5}$
GW	950
VOct	$6x10^{-6}$
VW	$1x10^{-5}$
Gut transport HL, $\boldsymbol{\tau_{trans}}$ (h)	8
Gut reaction HL, $\boldsymbol{\tau_{rxn}}$ (h)	$1x10^{12}$

4.3 Descriptors in the model

The parameters describing the model and its default parameterization are provided in Section 4.2 and outlined in Arnot et al., 2023 [5]. The biological and system parameters are fixed in the model and cannot be changed by the user. The model requires chemical-specific K_{OW}, K_{OA}, pka (for IOCs), and HL_B values.

4.4 Descriptor selection

EAS-E Suite is designed to search built-in databases of experimental or predicted input parameters based on user input CAS, name or SMILES. In EAS-E Suite the user can also enter preferred values for K_{OW} K_{OA}, pka, and HL_B and use *in vitro* biotransformation rate data and built in IVIVE models to calculate HL_B.

4.5 Algorithm and descriptor generation

A 1Co-PBK mass balance model for calculating BMFs and HL_T in rat is described in Section 4.2.

4.6 Software name and version for descriptor generation

4.7 Descriptors/Chemicals ratio

5 DEFINING THE APPLICABILITY DOMAIN: OECD PRINCIPLE 3

5.1 Description of the applicability domain of the model

Currently there is no universally accepted definition to characterize the Applicability Domain (AD) of 1Co-PBK mass balance models.

5.2 Method used to assess the applicability domain assessment

5.3 Software name and version for applicability of domain assessment

5.4 Limits of applicability

The model predictions may be highly uncertain for chemicals that have estimated log K_{OW} values above 9 because there are very few chemicals with measured K_{OW} values > 9 and the chemical dietary uptake efficiency estimate is very sensitive to K_{OW} in the range log K_{OW} 8 to 12. Biopartitioning of IOCs is not well defined for many classes of IOCs and scaling factors are assumed for scaling partitioning properties from the neutral form of K_{OW} to the charged form. EAS-E Suite users can change these scaling factors. EAS-E Suite users can also enter chemical-specific biopartitioning data for the neutral and charged forms of chemicals, if such data are available. The model is generally not recommended for pigments and dyes, quaternary ammonium chemicals, or for perfluorinated alkyl acids because the biopartitioning of these chemicals is highly uncertain. The model assumes that passive chemical uptake and elimination dominates over any active secretion or resorption processes in the kidney. The model is not recommended for chemicals that are subject to significant active secretion or resorption processes in the kidney.

6 DEFINING GOODNESS OF FIT AND ROBUSTNESS: OECD PRINCIPLE 4

6.1 Availability of the training set

There is no training data set for the model. The equations are developed from theory and from different datasets used to characterize chemical uptake and elimination rates in a rat.

6.2 Available information for the training set

Not Applicable

6.3 Data for each descriptor variable for the training set

Not Applicable

6.4 Data for the dependent variable (response) for the training set

Not Applicable

6.5 Robustness – statistics

Not Applicable

7 DEFINING PREDICTABILITY: OECD PRINCIPLE 4

7.1 Availability of external evaluation ("validation") set

The external evaluation set used in this QMRF are the critically evaluated laboratory HL_T data. It is emphasized that mass balance models like these cannot technically be "validated" in the same manner a QSAR can be validated; hence the term evaluation is used instead.

7.2 Available information for the external evaluation set

7.3 Data for each descriptor variable for the external evaluation set

7.4 Data for the dependent variable for the external evaluation set

7.5 Other information about the external evaluation set

7.6 Experimental design of test set

7.7 Predictivity – statistics obtained by external evaluation

Figure 7.1 shows the 1Co-PBK rat model calculated HL_T parameterized with HL_B-QSAR consensus predictions for humans (scaled to rat body mass) compared to a dataset of measured HL_T. The high quality dataset does not include studies that only used TRR and other experimental errors that were identified in the data quality analysis. 80% of the predicted HL_Ts are within a factor of 10 of observed "high quality" HL_Ts. This illustrates one way in which the model performance can be evaluated. It can also be evaluated with other methods for estimating HL_B.

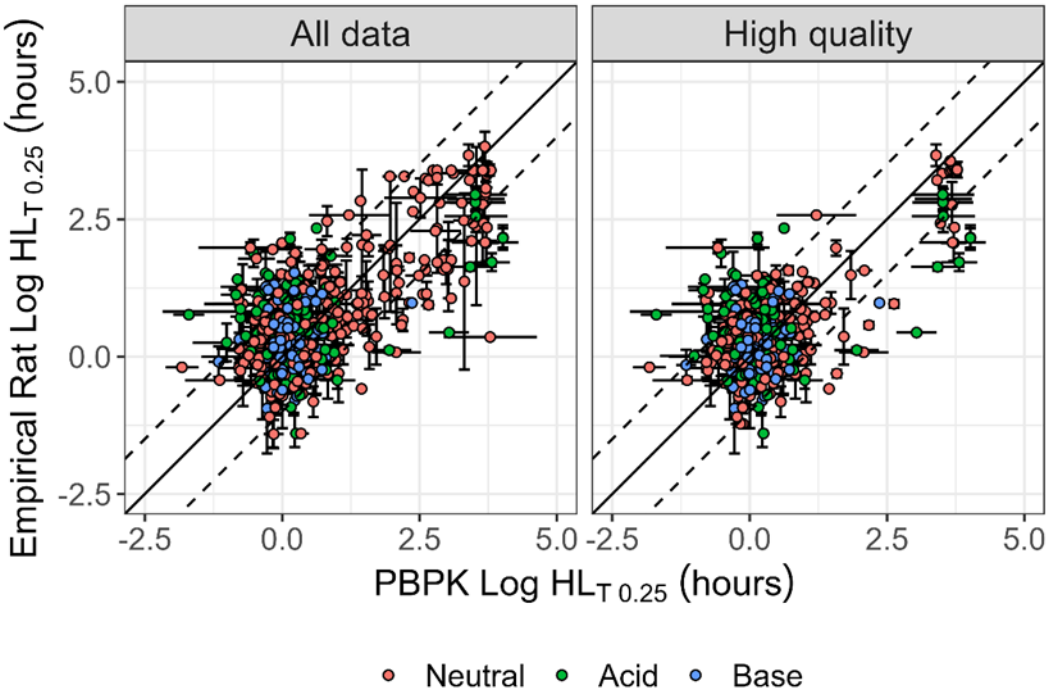

Figure 7.1 **An example of an evaluation of the 1Co-PBK rat model parameterized with HL_B-QSAR predictions derived from human data using available HL_T data for rats.**

7.8 Predictivity – assessment of the external evaluation set

Table 7.1 summarizes model performance statistics for the model evaluation data sets shown in **Figure 7.1**. CCC is the concordance correlation coefficient, RMSE is root mean standard error, MAE is Mean Absolute Error, and MB is model bias.

Model Bias is calculated as:

$$MB = \frac{\sum(\log Predicted - \log Observed)}{n}$$

where *Predicted* is the model value and *Observed* is the measured or reported value. Positive values of MB indicated overestimation of the observed value whereas negative values of MB indicate underestimation. The Mean Absolute Error (MAE) is calculated using the absolute values of the residuals.

$$MAE = \frac{\sum|(\log Predicted - \log Observed)|}{n}$$

The statistics in **Table 7.1** are on a $\log_{10}$ basis. The MB of -0.10 then means the 1Co-PBK rat model calculated HL_T values are *on average* a factor of 0.79 (i.e., $10^{-0.1}$) less than observations.

Table 7.1. Summary statistics of the 1Co-PBK rat model evaluation (shown in Figure 7.1).

Evaluation dataset	n	CCC	r	r^2	RMSE	MAE	MB
All data	**538**	**0.73**	**0.75**	**0.56**	**0.84**	**0.66**	**-0.10**
High quality	**391**	**0.63**	**0.65**	**0.42**	**0.81**	**0.63**	**-0.14**

7.9 Comments on the external evaluation of the models

The statistical evaluations of the BMF and HL_T model conducted here are unpublished and were prepared for this QMRF document.

8 PROVIDING A MECHANISTIC APPROACH – OECD PRINCIPLE 5

8.1 Mechanistic basis of the models

The 1Co-PBK rat model includes mechanistic processes for biomagnification such as chemical uptake from its diet and chemical elimination from respiration, faecal egestion, urinary excretion, growth dilution and biotransformation.

8.2 *A priori* or *a posteriori* mechanistic interpretation

9 MISCELLANEOUS INFORMATION

9.1 Comments

9.2 Bibliography

1. OECD, *Test No. 305: Bioaccumulation in Fish: Aqueous and Dietary Exposure*, in *OECD Guidelines for the Testing of Chemicals, Section 3*. 2012, Organisation for Economic Cooperation and Development Paris, France.
2. Arnot, J., B. Birk, P. Curtis-Jackson, F.A.P.C. Gobas, K.-U. Goss, M. Habekost, D. Hirmann, V. Bonnomet, T. Hofer, S. Jacobi, S. Krause, H. Laue, M. Laurentie, A.M. Aparicio, M. van der Mescht, C. Rauert, G. Treu, A. Redman, L.J. Saunders, E. Verbruggen, F. Wania, and P. Whalley, *Bioaccumulation assessment of air-breathing mammals: a discussion paper*. 2022, European Chemical Agency (ECHA): Helsinki. p. 46.
3. OECD, *Toxicokinetics. OECD 417 Guidelines for Testing Chemicals.* 2010, Organization for Economic Co-operation and Development: Paris.
4. Hoke, R., D. Huggett, S. Brasfield, B. Brown, M. Embry, A. Fairbrother, M. Kivi, M.L. Paumen, R. Prosser, D. Salvito, and R. Scroggins, Review of laboratory-based terrestrial bioaccumulation assessment approaches for organic chemicals: Current status and future possibilities. Integrated Environmental Assessment and Management, 2016. **12**(1): p. 109-122.
5. Arnot, J.A., L. Toose, J.M. Armitage, M. Embry, A. Sangion, and L. Hughes, A weight of evidence approach for bioaccumulation assessment. Integrated Environmental Assessment and Management, 2023. **19**(5): p. 1235–1253.
6. Armitage, J.M. and F.A.P.C. Gobas, A terrestrial food-chain bioaccumulation model for POPs. Environmental Science & Technology, 2007. **41**: p. 4019 - 4025.
7. Kelly, B.C., M.G. Ikonomou, J.D. Blair, A.E. Morin, and F.A. Gobas, Food web-specific biomagnification of persistent organic pollutants. Science, 2007. **317**(5835): p. 236-9.
8. Arnot, J.A., T.N. Brown, F. Wania, K. Breivik, and M.S. McLachlan, Prioritizing chemicals and data requirements for screening-level exposure and risk assessment. Environmental Health Perspectives, 2012. **120**(11): p. 1565-1570.
9. Armitage, J.M., L. Hughes, A. Sangion, and J.A. Arnot, Development and intercomparison of single and multicompartment physiologically-based toxicokinetic models: Implications for model selection and tiered modeling frameworks. Environment International, 2021. **154**: p. 106557.
10. U.S. EPA, *Exposure Factors Handbook.* 1997, U.S. Environmental Protection Agency: Washington, DC. p. 1193.
11. Hickie, B., D. Mackay, and J. de Koning, Lifetime Pharmacokinetic Model for Hydrophobic Contaminants in Marine Mammals. Environmental Toxicology and Chemistry, 1999. **18**(11): p. 2622-2633.
12. Schmitt, W., General approach for the calculation of tissue to plasma partition coefficients. Toxicol In Vitro, 2008. **22**(2): p. 457-67.
13. Endo, S. and K.-U. Goss, Serum albumin binding of structurally diverse neutral organic compounds: data and models. Chemical Research in Toxicology, 2011. **24**(12): p. 2293-2301.

14. Arnot, J.A. and D. Mackay, The influence of chemical degradation during dietary exposures to fish on biomagnification factors and bioaccumulation factors. Environmental Science: Processes & Impacts, 2018. **20**(1): p. 86 - 97.
15. Arnot, J.A. and F.A.P.C. Gobas, A food web bioaccumulation model for organic chemicals in aquatic ecosystems. Environmental Toxicology and Chemistry, 2004. **23**(10): p. 2343-2355.
16. Kelly, B.C., F.A.P.C. Gobas, and M.S. McLachlan, Intestinal Absorption and Biomagnification of Organic Contaminants in Fish, Wildlife, and Humans. Environmental Toxicology and Chemistry, 2004. **23**(10): p. 2324-2336.
17. Gobas, F.A.P.C., J.B. Wilcockson, R.W. Russell, and G.D. Haffner, Mechanism of biomagnification in fish under laboratory and field conditions. Environmental Science and Technology, 1999. **33**(1): p. 133-141.
18. Armitage, J.M., R.J. Erickson, T. Luckenbach, C.A. Ng, R.S. Prosser, J.A. Arnot, K. Schirmer, and J.W. Nichols, Assessing the bioaccumulation potential of ionizable organic compounds: Current knowledge and research priorities. Environ Toxicol Chem, 2017. **36**(4): p. 882-897.
19. Arnot, J.A., L. Toose, J.M. Armitage, A. Sangion, A. Looky, T.N. Brown, L. Li, and R.A. Becker, Developing an internal threshold of toxicological concern (iTTC). Journal of Exposure Science & Environmental Epidemiology, 2022. **32**(6): p. 877-884.
20. Papa, E., A. Sangion, J.A. Arnot, and P. Gramatica, Development of human biotransformation QSARs and application for PBT assessment refinement. Food and Chemical Toxicology, 2018. **112**: p. 535-543.
21. Arnot, J.A., T.N. Brown, and F. Wania, Estimating screening-level organic chemical half-lives in humans. Environmental Science and Technology, 2014. **48**: p. 723-730.