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Estimating Screening-Level Organic Chemical Half-Lives in Humans

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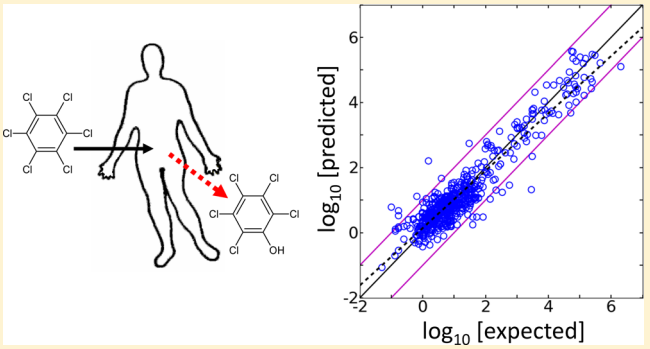
Supporting Information

ABSTRACT: Relatively few measured data are available for the thousands of chemicals requiring hazard and risk assessment. The whole body, total elimination half-life (HL_T) and the whole body, primary biotransformation half-life (HL_B) are key parameters determining the extent of bioaccumulation, biological concentration, and risk from chemical exposure. A one-compartment pharmacokinetic (1-CoPK) mass balance model was developed to estimate organic chemical HL_B from measured HL_T data in mammals. Approximately 1900 HLs for human adults were collected and reviewed and the 1-CoPK model was parametrized for an adult human to calculate HL_B from HL_T. Measured renal clearance and whole body total clearance data for 306 chemicals were used to calculate empirical $HL_{B,emp}$. The $HL_{B,emp}$ values and other measured data were used to corroborate the 1-CoPK HL_B model calculations. HLs span approximately 7.5 orders of magnitude from 0.05 h for nitroglycerin to 2×10^6 h for 2,3,4,5,2′,3′,5′,6′-octachlorobiphenyl with a median of 7.6 h. The automated Iterative Fragment Selection (IFS) method was applied to develop and evaluate various quantitative structure−activity relationships (QSARs) to predict HL_T and HL_B from chemical structure and two novel QSARs are detailed. The HL_T and HL_B QSARs show similar statistical performance; that is, r^2 = 0.89, $r^{2\text{-ext}}$ = 0.72 and 0.73 for training and external validation sets, respectively, and root-mean-square errors for the validation data sets are 0.70 and 0.75, respectively.



INTRODUCTION

Chemical management and regulatory programs seek to protect human health and the environment. Biomonitoring data for some known contaminants provide valuable information for human exposure and risk assessment.[1] Biomonitoring data can also be used to calculate chemical intake (exposure) rates and infer exposure pathways if the whole body, total elimination half-life (HL_T; h), or the corresponding first-order total elimination rate constant (k_T; h^{-1}) is available.[2] The exposure duration required to approach steady-state is determined by HL_T and is therefore necessary for interpreting biomonitoring data and exposures. Because of measurement data gaps, mass balance models and quantitative structure−activity relationships (QSARs) are required to screen thousands of chemicals for more comprehensive evaluations.[3−5] One-compartment pharmacokinetic (1-CoPK) models are frequently used and require HL_T or the whole body, primary biotransformation (metabolism) first-order rate constant (k_B; h^{-1}), or the corresponding biotransformation half-life (HL_B; h) as an input parameter.[5−8]

Because of k_B data gaps, screening-level bioaccumulation and exposure assessments often assume k_B = 0. For example, 1-CoPK models parametrized assuming k_B = 0 hypothesize that neutral organic chemicals with octanol−water partition coefficients (K_{OW}; unitless) $>10^2$ and octanol−air partition coefficients (K_{OA}; unitless) $>10^6$ have the potential to biomagnify in air-breathing organisms.[9−12] The k_B = 0 assumption can result in overestimates of bioaccumulation and exposure for chemicals subject to biotransformation.[6,13] Furthermore, when examining human bioaccumulation and exposure from a multimedia perspective k_B is shown to be of relatively greater importance than the chemical's partitioning properties.[7] Uncertainties associated with HL_B typically contribute the greatest uncertainty in the overall assessment of human bioaccumulation and exposure potential.[5,8] In vitro-to-in vivo extrapolation (IVIVE) methods are used to estimate biotransformation half-lives for pharmaceuticals[14] and for high-throughput exposure and risk assessment.[15] Corroborating IVIVE estimates with in vivo and in silico biotransformation rate estimates would provide greater confidence in all

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estimation methods. The parameter HL_T has also been proposed as a criterion for bioaccumulation hazard assessment, and following such an approach HL_B data are required for higher tier assessments.[16] A method to estimate HL_B from measured fish bioaccumulation data,[17] a fish HL_B database,[18] and HL_B QSARs for fish[19,20] have been developed. Complementary methods, databases, and QSARs for in vivo HL_T and HL_B estimates for mammals and other air-breathing organisms are needed.

Here we develop and evaluate databases and screening-level HL_T and HL_B QSARs for organic chemicals in humans. We collect human HL data and evaluate these data for their suitability for developing fragment-based QSARs. When measured renal clearance and HL_T data are available for the same chemical we calculate empirical $HL_{B,emp}$ values. We develop and evaluate a general 1-CoPK model to calculate HL_B from measured HL_T data in mammals and we parametrize the model for humans to generate new HL_B databases. We use the HL_T and HL_B databases to develop and validate a series of QSARs and present details for two selected QSARs; one for HL_T and one for HL_B. We discuss potential applications of the QSARs and future research needs to address uncertainty in HL prediction.

METHODS

First-order kinetics are assumed; that is, $k = \ln 2/HL$, and HLs are selected as the property of interest for the database and QSAR development. Primary biotransformation is defined here as the conversion (elimination) of the parent chemical through reaction into another chemical (metabolite), including conjugation with endogenous molecules. Other processes that eliminate the parent chemical from an organism include respiratory elimination, renal excretion, and fecal egestion. For chemicals with long HLs organism growth may also contribute to lower measured whole body concentrations over time.

Figure 1 outlines the general methods used to compile and derive various databases for the development and validation of

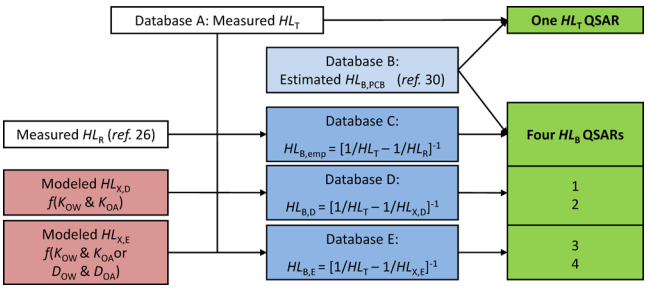

Figure 1. Whole body, total elimination half-life (HL_T) and whole body, primary biotransformation half-life (HL_B) databases (A through E) used to develop and validate quantitative structure−activity relationships (QSARs). Clear boxes denote existing measured HL_T (Database A) and renal clearance half-life (HL_R) data; light blue box denotes existing HL_B estimates for polychlorinated biphenyls (PCBs), Database B; red boxes denote model predictions for chemical half-life in a representative human adult in the absence of biotransformation (HL_X) as parametrized using the octanol−water partition coefficient (K_{OW}) and the octanol−air partition coefficient (K_{OA}) or the octanol−water distribution coefficient (D_{OW}) and the octanol−air distribution coefficient (D_{OA}); dark blue boxes denote new HL_B databases developed in the present study (C, D, and E), and green boxes highlight five new QSARs.

HL_T and HL_B QSARs. We searched the peer-reviewed literature and public sources of pharmacokinetic and toxicokinetic information to compile HL databases for organic chemicals in human adults. We obtained simplified molecular-input line entry system (SMILES) notations [21] either from the original HL data sources or from CAS registration number or chemical name searches. Canonical SMILES were derived using OpenBabel V.2.3.2 (www.openbabel.org).[22] Chemicals containing ionic salts were treated as the discrete organic chemical by removing the inorganic counterion in the SMILES notation.

***HL_T* QSAR: Databases A and B.** Two databases form the basis of the HL_T QSAR training and testing sets. Database A consists of measured or estimated adult HL_T values. Two key sources of measured HL_T for pharmaceuticals are DrugBank (version 2.5), an online source (www.drugbank.ca)[23,24] maintained at the University of Alberta (Edmonton, AB, Canada) and data compilations by Obach, Varma, and colleagues.[25,26] These sources report data quality assurance methods and have been peer-reviewed. Key sources of HL_T data for environmental contaminants included the peer-reviewed literature, for example, refs 27−29 and the peer-reviewed online database TOXNET (http://toxnet.nlm.nih.gov/) maintained in the National Library of Medicine by the National Institutes of Health (Bethesda, MD, USA). Database B is a human polychlorinated biphenyl (PCB) $HL_{B,PCB}$ database.[30] Because that study already addressed nonmetabolic loss processes and did not provide HL_T estimates we assume $HL_{B,PCB} \approx HL_{T,PCB}$ for QSAR development and evaluation.

Humans are often continuously exposed to environmental contaminants, albeit at low concentrations, and it is noted that continued exposure can confound the derivation of accurate HLs for certain environmental contaminants such as PCBs. Some of the HL_T [29] and HL_B [30] estimates for persistent environmental contaminants have been subjected to methods elsewhere to address continued exposures through environmental sources and we included these "corrected" HL estimates in our QSAR databases. For some of the persistent environmental contaminants the HL_T values do not address continued exposure. In general, HLs for persistent environmental contaminants are long (years) and remaining potential errors in HL_T for these chemicals for which the corrections were not applied are assumed to be relatively minor in the context of the current QSAR objectives.

***HL_B* QSAR: Databases B and C.** Four databases form the basis of the HL_B QSAR training and testing sets. The first HL_B database (Database B) is the previously mentioned $HL_{B,PCB}$ database.[30] HL_T values for the different PCB congeners were not reported; therefore, it is not possible to apply our HL_B estimation methods to these data. The second HL_B database (Database C) includes 306 chemicals with measured HL_T in Database A for which there are also empirical estimates of renal clearance.[26] We calculate empirical $HL_{B,emp}$ estimates as

$$HL_{B,emp} = [1/HL_T \times (1 - Cl_R/Cl_T)]^{-1} = [1/HL_T - 1/HL_R]^{-1} \quad (1)$$

where Cl_R is renal clearance (mL/min/kg), Cl_T is total whole body clearance (mL/min/kg) and HL_R is the renal excretion half-life (h), that is, $HL_T/(Cl_R/Cl_T)$. Equation 1 neglects respiratory and fecal excretion pathways. Other elimination processes are assumed to be relatively small by comparison,[15] and this assumption is examined later. For 11 other chemicals in Database A for which HL_R data exist, $Cl_R = Cl_T$ indicating

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comparatively negligible nonrenal clearance; therefore, $HL_{B,emp}$ could not be calculated for these chemicals. When Cl_R is only slightly smaller than Cl_T, the $HL_{B,emp}$ estimate may be more uncertain than when Cl_R is much smaller than Cl_T.

Mass Balance HL_B Estimation Method. We developed a 1-CoPK model to estimate HL_B (k_B) from HL_T (k_T) data for mammals based on a conceptual approach for estimating HL_B (k_B) from measured experimental bioaccumulation testing data in fish.[17] The 1-CoPK model calculates rate constants for the assumed major processes of parent chemical elimination from the body other than biotransformation. The model then sums these rate constants in the term k_X and subtracts k_X from k_T to obtain estimates of k_B on a chemical- and study-specific basis; that is, $k_B = k_T - k_X$. In terms of *HL*s the calculation is

$$HL_B = [1/HL_T - 1/HL_X]^{-1} \quad (2)$$

Assumptions of a whole body, first-order kinetics model and the treatment of only passive (diffusion-based) elimination processes are uncertainties with the current approach; however, the method includes screening-level uncertainty analyses for the HL_B calculations to address some of the uncertainty in the model, data used to parametrize the model, and measured HL_T data. The uncertainty analysis is also included to interpret the general reliability of the HL_B estimates and guide data selection for QSAR development. Details of the HL_B estimation model, parametrization, and uncertainty analysis are in the Supporting Information (SI, section 1).

***HL_B* QSAR: Databases D and E.** We parametrized the HL_B estimation model for a reference human adult to calculate HL_B for chemicals with measured or estimated human adult HL_T values in Database A (SI, section 2). We first parametrized the model using partitioning information for the neutral form of all chemicals only, K_{OW} and K_{OA}, to calculate $HL_{X,D}$ and to obtain Database D ($HL_{B,D}$). We then parametrized the model using estimates of the distribution coefficients, D_{OW} and D_{OA}, for ionogenic organic chemicals (IOCs) that are expected to be appreciably ionized at physiological pH (7.4) to calculate $HL_{X,E}$ and to obtain Database E ($HL_{B,E}$). Chemicals ≥33% in their ionic form at pH 7.4 were considered appreciably ionized. HL_Bs for neutral organic chemicals included in Database E were estimated using K_{OW} and K_{OA}. Parameterizing the model with distribution coefficients to obtain Database E allows the examination of different HL_X estimates for IOCs, particularly for renal excretion, HL_R. We compared HL_B estimates in Databases D and E to $HL_{B,emp}$ estimates (Database C) to corroborate the estimation methods and to guide the selection of 1-CoPK HL_B estimates for QSAR development.

QSAR Development and Evaluation. Iterative Fragment Selection (IFS) is an automated method for QSAR development and evaluation.[20] The QSAR methods applied here follow standard Organisation for Economic Cooperation and Development (OECD) guidance for QSAR development and validation.[31,32] The IFS method creates group contribution QSARs for chemical property and activity prediction using a pool of descriptors (groups or fragments) generated from a training data set. The domain of applicability for an IFS-generated QSAR is defined using a nearest-neighbors approach to measure the similarity of a chemical to the structure and properties of chemicals in the training data set, referred to here as a chemical similarity score (CSS). An external testing data set is used to validate the models, and to estimate the uncertainty of the predictions based on the degree to which a chemical falls within the domain of applicability.[20] The IFS procedure and technical details can be found elsewhere.[20] A general multiple linear regression model for *HL* is defined as

$$\log_{10} HL_j = a_0 + a_1 f_1 + a_2 f_2 + \ldots + a_n f_n + e_j \quad (3)$$

where $\log_{10} HL_j$ is the base 10 logarithm of the *HL* for the *j*th chemical, a_0 is the intercept, a_n is the regression coefficient for the molecular descriptor *n*, f_n is the number of the *n*th molecular descriptor (groups or fragments) in the *j*th chemical, and e_j is the error term and the overall mean error is equal to zero. Fragments are provided as SMiles ARbitrary Target Specification (SMARTS)[33] (www.daylight.com) and regression coefficients were estimated by the method of least-squares. For IOCs only the neutral form of the chemical is considered for chemical descriptors. We developed several QSARs using different subsets of the *HL* data and explored different *k* levels ("leave many out cross-validations") and different ratios of training and testing (external validation) data splits. We decided that a balanced approach to model training and characterizing uncertainty in model predictions was to use 50:50 data splits.

RESULTS AND DISCUSSION

***HL* Data Compilation.** The objective of the *HL* data collection is to obtain a variety of discrete organic chemical structures with a range of *HL* values for developing and evaluating QSARs. We initially compiled approximately 1900 measured or estimated *HL*s for chemicals in human adults. Approximately 380 *HL*s were deemed inappropriate for the current objectives of developing fragment-based screening-level *HL* QSARs for xenobiotics and were not used. Examples of these chemicals include endogenous molecules (hormones, neurotransmitters), metallic compounds, tautomers, and large macrocyclic molecules (details in SI, section 3). Approximately 410 *HL*s are repeated values from different data sources for the same chemical (pharmaceuticals). Another approximately 160 entries are different *HL*s for the same chemical (environmental contaminants) and it is necessary to select a single value for QSAR development; therefore, geometric means were calculated for these chemicals. The fragment method does not recognize differences in stereoisomers; therefore, in a few cases a geometric mean was also used when *HL*s for more than one stereoisomer were available. Screening-level QSAR predictions for stereoisomers need to be interpreted cautiously.

***HL_T* Database.** This evaluation resulted in a data set of 1105 chemicals for HL_T QSAR development with molar mass ranging from 30 (formaldehyde) to 960 (decabromodiphenyl ether) g/mol. The *HL*s span approximately 7.5 orders of magnitude from 0.05 h (0.002 d) for nitroglycerin to 2×10^6 h (83 000 d) for 2,3,4,5,2′,3′,5′,6′-octachlorobiphenyl with a median of 7.6 h (0.32 d). The corresponding rate constants range from 14/h (330/d) to 3.5×10^{-7}/h (8.3×10^{-6})/d with a median of 0.091/h (2.2/d). Eighty percent of the chemicals in the HL_T QSAR data set are pharmaceuticals (measured HL_T) and 20% are environmental contaminants (estimated or assumed to approximate HL_T). The chemicals in the HL_T QSAR data set form the basis from which the HL_B QSAR data sets are derived.

***HL_X* Calculations.** The 1-CoPK model calculated whole body half-life for a chemical as a result of passive renal excretion, fecal egestion, respiratory elimination, and growth dilution, that is, elimination processes excluding primary biotransformation, is HL_X. Figure 2 displays with different

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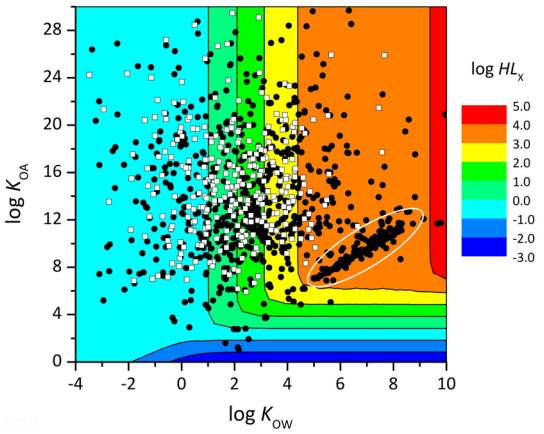

Figure 2. One-compartment pharmacokinetic model calculations for chemical half-life in a representative human adult in the absence of biotransformation (HL_X; d) as a function of the octanol−water partition coefficient (K_{OW}) and the octanol−air partition coefficient (K_{OA}). Predicted HL_X values progress from short half-lives (blue colors) to long half-lives (red colors). Chemicals in Databases A (black circles), B (black circles in white oval) and C (white squares) are superimposed based on their partitioning properties.

colors the calculated HL_X as a function of the partitioning space defined by K_{OW} and K_{OA}; chemicals in Databases A and B are superimposed on this space. The depicted HL_X values span from about 0.036 h (0.0015 d) to 8.3×10^5 h (35 000 d) or about 7.5 orders of magnitude. The shortest HL_X (fastest rates) for passive chemical elimination from the body are for chemicals with log K_{OA} of approximately ≤1 and log K_{OW} > 0. These volatile chemicals also have relatively high air−water partition coefficients and respiration of air is a highly effective route of elimination. There are no chemicals with these partitioning properties in Database A; however, there are a few chemicals with relatively low K_{OA} and high K_{AW} that are eliminated relatively quickly through the respiratory process. For chemicals with log K_{OA} > 3 and log K_{OW} < 1 renal excretion is dominant and a relatively fast elimination process. Many chemicals in Database A with these properties also include empirical estimates for renal clearance (Figure 2: white squares, Database C). The 1-CoPK model predicts that renal excretion and fecal egestion *HL*s become similar (~2 000 d) for chemicals with a log K_{OW} ~4.5 with passive renal excretion *HL*s showing continued increases with increasing K_{OW}. Fecal egestion dominates HL_X for chemicals with log K_{OW} > ~5 and log K_{OA} > ~6; however, passive elimination for these chemicals is slow and the corresponding HL_Xs are long (years).

The 1-CoPK model shows a general trend of increasing HL_X (decreasing rates of passive chemical elimination) with increasing K_{OW} and increasing K_{OA}, that is, moving toward the right and top of the figure, as a result of decreasing water solubility (renal excretion) and volatility (respiratory elimination). In this context the model calculations are in general agreement with other 1-CoPK models used to screen for bioaccumulation, biomagnification[7,8,10] and total elimination[16] in humans. In particular, in the absence of biotransformation and active chemical elimination processes, chemicals with log K_{OW} > ~3 and log K_{OA} > ~5 have HL_X > ~70 d (k_X < ~0.01/d) (e.g., ref 16) and consequently biomagnification potential in humans. There are thousands of chemicals with these partitioning properties (e.g., ref 9) emphasizing the need to develop HL_B databases and QSARs.

***HL_B* Databases.** The HL_B estimates in Databases D and E were calculated from HL_T measurements in Database A. The possibility for error in calculating HL_B increases when values of HL_X and HL_T are similar. Five data confidence categories were derived from the screening-level uncertainty analysis for the HL_B calculations (SI, section 3). Confidence category 1 data are considered to be less uncertain than category 2 data and so on; however, it is still possible that a HL_B estimate in a lower confidence category (e.g., 4) is of comparable or better quality than a HL_B estimate in a higher confidence category (e.g., 1). When measured HL_T and estimated HL_X have substantial overlap in their distributions or $HL_X > HL_T$, reliable estimates of HL_B could not be obtained and were assigned to confidence category 5. For many chemicals (30−50%), the uncertainty in the HL_B estimate approximates the uncertainty assigned to the HL_T value, i.e. assumed uncertainty is ± a factor of 3 or a range of about 1 order of magnitude. In these cases model calculations and physical-chemical properties add relatively little additional uncertainty, that is, $HL_X \ll HL_T$; therefore, $HL_B \approx HL_T$ and the uncertainty in HL_B is comparable to the uncertainty in HL_T.

The $HL_{B,emp}$ estimates (Database C) were compared with 1-CoPK HL_B estimates in Databases D and E to corroborate the estimation methods and to guide the selection of different data sets for QSARs. Most 1-CoPK HL_B estimates in Databases D and E with confidence categories 1, 2, and 3 are in good agreement with the $HL_{B,emp}$ estimates; confidence category 1 data show the strongest agreement with the $HL_{B,emp}$ estimates (SI, Figure SI-1). The mass balance model estimation method for fecal egestion is also corroborated with some measured data for fecal egestion (SI, section 3); however, data sets for model evaluations of respiratory elimination are limited and this elimination process was therefore not evaluated. Fortunately, given the general partitioning properties of the chemicals in Database A, renal excretion and fecal egestion are expected to be the principal passive elimination processes competing with primary biotransformation processes for the large majority of the chemicals.

Figure 2 shows substantive overlap in the chemical partitioning space covered by chemicals in Database A with measured renal clearance data (white boxes) and those without such data (black circles). An exception to this overlap is the lower right quadrant of Figure 2 in which there are few $HL_{B,emp}$ estimates for chemicals such as PCBs and polychlorinated dioxins and furans; renal excretion is generally insignificant for such chemicals. Some nonrenal elimination of the parent chemical may also occur for some of the $HL_{B,emp}$ estimates; however, since the majority are low K_{OW} (95% < $10^{4.6}$) and D_{OW} (95% < $10^{3.3}$) chemicals and measured data show that most water-soluble chemicals are eliminated effectively through renal excretion,[26] we generally assumed these chemicals are predominantly eliminated either by renal excretion or through primary biotransformation and other rates of elimination are comparatively insignificant. We found strong agreement between the $HL_{B,emp}$ and HL_B estimates for hydrophobic chemicals (SI, Figure SI-2) supporting the simplified calculations for $HL_{B,emp}$ and the 1-CoPK model HL_B estimates; however, there is a need to develop more sophisticated descriptions for renal excretion in 1-CoPK models, particularly for chemicals subject to active uptake and elimination processes.

The PCBs in Figure 2 are in a region of the chemical partitioning space that shows low rates of predicted passive

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chemical elimination, 1,000 d < HL_X < 10,000 d, providing assurance for our assumption that the $HL_{B,PCB}$ data from Brown [30] can be used in both the HL_T and HL_B QSARs; that is, $HL_B \approx HL_T$. This assumption is supported by a statistical comparison of $HL_{B,PCB}$ data derived by Brown [30] and HL_Bs derived here from different HL_T sources for the same 17 congeners (two-tailed t test, $p = 0.062$).

HL_B QSAR Data Sets. On the basis of these evaluations and a desire to balance uncertainty (error) in HL estimates with limited data availability, 1-CoPK HL_B estimates with confidence categories 1 and 2 data were initially selected for QSAR development and HL_B estimates with confidence categories 3 and 4 were set aside. $HL_{B,emp}$ estimates ($n = 306$) were used preferentially to 1-CoPK HL_B estimates for the HL_B QSARs. Database B $HL_{B,PCB}$ estimates were used directly, unless there was another HL_B estimate available in Database D or E for the same PCB congener, in which case the geometric mean was used. Initial HL_B QSAR data sets 1 and 3 contain 1011 and 935 chemicals, respectively. HL_B QSAR data sets 1 and 3 have the same minima and maxima as the HL_T QSAR data set because the passive elimination of nitroglycerin from the body is negligible compared to the rate of reaction in the body, and the reported HL for 2,3,4,5,2′,3′,5′,6′-octachlorobiphenyl was already corrected for nonmetabolic losses.[30] The medians for initial HL_B QSAR data sets 1 and 3 are 9.5 h (0.39 d) and 9.3 h (0.39 d), respectively. Database E (QSAR data set 3) has fewer chemicals than Database D (QSAR data set 1) because the renal excretion rate constants are generally faster for IOCs when ionization is accounted for; hence, HL_X is smaller and there are fewer reliable HL_B estimates.

After the development of the initial HL_B QSARs we examined some other QSARs using different iterations of the databases. Some perfluorinated IOCs have relatively long biological HLs, are globally distributed in humans and wildlife[1,34] and the toxicokinetics of these chemicals are not well understood; particularly with respect to the possible occurrence of active reabsorption processes in the kidney and specific protein binding interactions.[35] By overestimating renal excretion and possibly underestimating biological sorption capacity for some of these chemicals, the 1-CoPK models underestimate HL_X for these substances; that is, reliable HL_Bs could not be calculated (confidence category 5). One objective of the screening-level QSARs developed here is to identify chemicals with long biological HLs; therefore, the HL_Ts for five perfluorinated chemicals in Database A were included as HL_Bs to derive the HL_B QSAR data sets number 2 (1015 chemicals, based on Databases B, C, and D) and number 4 (940 chemicals, based on Databases B, C, and E). The merits and disadvantages of using smaller data sets with more stringent data quality criteria were explored by developing additional QSARs. The smaller empirical data sets inevitably resulted in narrower domains of applicability and they did not result in reduced prediction error. We selected QSARs that retain a reasonably large domain of applicability without sacrificing the accuracy of predictions through the inclusion of data of questionable reliability.

QSAR Evaluations. Table SI-5 (SI, section 4) highlights general consistencies in the statistics for the five QSARs. All of the coefficients of determination for external validation (testing) sets ($r^{2\text{-ext}}$) are ≥0.7, a desirable quality for QSAR validation and for regulatory purposes.[31] The Akaike information criterion corrected for sample size (AIC_C) values are relatively low (<−500) and the concordance correlation coefficients (CCC) are relatively high (~0.9). The root-mean-square errors (RMSE) for the training sets (0.45 to 0.49 log units) and for the external validation sets (0.70 to 0.75 log units) are similar. The classification performance of the models for identifying chemicals with HLs ≥ 70 days or HLs < 70 days was also considered.[16] For example, using the combined training and testing data sets to evaluate model classification performance the sensitivity (true positive rate) of the QSARs ranges from 0.86 to 0.90, and the specificity (true negative rate) of the QSARs are 0.99 (see SI, Table SI-5 for more).[31] Given the general similarities in key statistics, determining which HL_B QSAR represents the best model is challenging. All models have merits and limitations; therefore, we also considered the domain of applicability statistics. The number of chemicals without fragments in the training sets ranges from 1 to 9. The number of validation chemicals without fragment overlap with chemicals in the training sets ranges from 1 to 7. On the basis of inspection of the statistics and the fragments selected by the IFS method and professional judgment, two QSARs were selected for further discussion (SI, section SI-4).

HL_T QSAR. Figure 3 compares the HL_T QSAR predicted HL_Ts (h) with expected (empirical) HL_Ts for training and testing (external validation) data sets and includes summary statistics. The common QSAR performance statistics r^2, $r^{2\text{-ext}}$, and RMSE are 0.89, 0.72, and 0.70, respectively; 97% and 77%, and 86% and 53% of the predicted values are within a factor of 10 and 3 of the expected values for the training and testing sets, respectively. It is desirable to obtain information on the applicability domain of a QSAR. Smaller circles in the testing set figure (right panel) reflect greater chemical similarity of the chemical to the chemicals in the training set. Supporting Information Figure SI-3 illustrates how the validation set determines the domain of applicability for the HL_T QSAR; the estimation of the variance in the predicted values based on structural similarity to chemicals in the training data set provides screening-level uncertainty estimates for the predicted HLs.[20] Supporting Information Table SI-6 lists the 63 SMARTS fragments (molecular descriptors) selected by the IFS method, the regression coefficients, associated standard errors, minimum and maximum counts of the fragment in

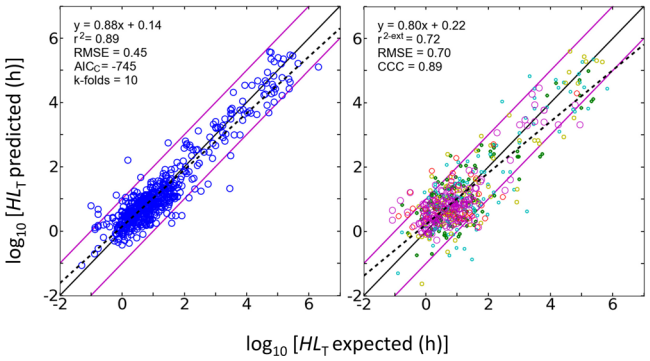

Figure 3. Comparison of whole body, total elimination half-life predictions (HL_T; h), and expected values for the training set (left) and external validation set (right). The different circle sizes and colors reflect designation to one of five different categories for the chemical similarity score of the test set chemical to the training data set chemicals; the smallest circles represent the greatest chemical similarity (>75%) and the largest circles represent the lowest chemical similarity (<5%). RMSE, root-mean-square error; CCC, concordance correlation coefficient; AIC_C, Akaike information criterion.

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chemicals, and the number of chemicals containing the fragment. Supporting Information Table SI-7 lists the HL_T QSAR training and testing sets.

***HL_B* QSAR.** Figure 4 compares the HL_B QSAR predicted HL_Bs (h) with expected (empirical) HL_Bs for training and

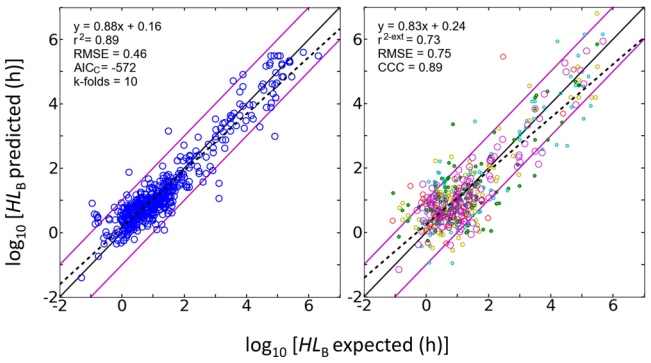

Figure 4. Comparison of whole body, primary biotransformation half-life predictions (HL_B; h) and expected values for the training set (left) and external validation set (right). The different circle sizes and colors reflect designation to one of five different categories for the chemical similarity score of the test set chemical to the training data set chemicals; the smallest circles represent the greatest chemical similarity (>75%) and the largest circles represent the lowest chemical similarity (<5%). RMSE: root-mean-square error; CCC: concordance correlation coefficient; AIC_C: Akaike information criterion.

testing (external validation) data sets and includes summary statistics. The recommended HL_B QSAR is based on HL_B data set number 4. The r^2, $r^{2\text{-ext}}$, and RMSE for this QSAR are 0.89, 0.73, and 0.75, respectively; 96% and 76%, and 82% and 52% of the predicted values are within a factor of 10 and 3 of the expected values for the training and testing sets, respectively. Supporting Information Figure SI-3 illustrates how the validation set determines the domain of applicability for the predicted HL_Bs. Supporting Information Table SI-8 lists the 62 fragments (molecular descriptors) selected by the IFS method, the regression coefficients, associated standard errors, minimum and maximum counts of the fragment in chemicals, and the number of chemicals containing the fragment. Supporting Information Table SI-9 lists the HL_B QSAR training and testing sets.

The RMSEs for neutral and predominantly neutral chemicals (<33% ionic form at pH 7.4) were compared with RMSEs for appreciably dissociated monoprotic IOCs (≥33% and <99.9% ionic form) and highly dissociated and potentially multiprotic IOCs (≥99.9% ionic form) and zwitterionic chemicals for the two selected QSARs (SI, Table SI-10). The RMSEs for IOCs ≥ 33% ionized are lower than RMSEs for the neutral and predominantly neutral chemical data set. These results are similar to findings with a fish HL_B QSAR in that comparisons of predictions with expected values for IOCs were generally as good or better than predictions for neutral chemicals.[20] The r^2 values and slopes are better for the human *HL* QSARs than for the fish HL_B QSARs, whereas the $r^{2\text{-ext}}$ values are quite similar.[19,20] The RMSEs for the human *HL* QSARs are slightly larger than values for fish HL_B QSARs (0.49 to 0.53 for training sets and 0.58 to 0.62 for testing sets).[19,20] The human *HL* data sets may be particularly challenging for QSARs because they comprise many structurally complex pharmaceuticals. While the prediction error is expected to be greater for the human *HL* QSARs than for the fish *HL* QSAR,[20] the quantitative information on prediction uncertainty provided by the IFS QSARs provides valuable guidance when interpreting and considering predictions for various applications.

Fragment Analysis. The diversity of the fragments and fragment counts (SI, Tables SI-6 and SI-8) reflect the structural diversity of the data sets and the selected QSARs. Differences between HL_T and HL_B for many chemicals are relatively small when HL_T is dominated by biotransformation. This explains some of the statistical similarity between the HL_T and HL_B QSARs; however, as highlighted in SI Tables SI-6 and SI-8, there are many molecular descriptors that are unique to one of the two selected QSARs. Some of the fragments lend themselves to mechanistic interpretation. Halogenation increases the *HL*s (HL_T and HL_B). Carbon−carbon double bonds generally increase the *HL*s with a few fragments canceling the effect in specific cases. Aliphatic carbons tend to increase the *HL*s; however, *HL* data for simple aliphatic hydrocarbons are lacking. Aromatic carbons tend to increase the *HL*; exceptions are aromatic carbon fragments specific to biphenyl-like molecules with negative coefficients that partially offset the positive coefficients of co-occurring halogens. Fragments containing nonaromatic nitrogen tend to increase the *HL*s and fragments containing heteroaromatic nitrogen tend to decrease the *HL*s. On average there are slightly more fragments with positive coefficients, but the fragments that have negative coefficients are more strongly negative. Interpreting all of the fragments in this context is somewhat difficult and limited because of the potential antagonistic and synergistic interaction of fragments on a particular chemical and further analysis is beyond the scope of the present study.

Common Outliers. Ten chemicals with *HL* predictions that differed from expected values by more than 2 orders of magnitude in either the training or testing sets for the two selected QSARs are listed in SI Table SI-11. The largest prediction error in the HL_T QSAR is for hexabromocyclododecane (2.6 log unit underprediction, in validation set, considered "in domain", stereoisomer) and the largest prediction error in the HL_B QSAR is for decabromodiphenyl ether (3.0 log unit overprediction, in validation set, considered "out of domain"). Acetazolamide is an outlier in the selected HL_B QSAR (2.1 log unit underfit, in training set), and upon closer inspection is a common outlier in many of the QSARs. Acetazolamide is a chemical that is almost entirely eliminated unchanged through renal excretion (CL_T = 0.65 and CL_R = 0.64 mL/min/kg [26]) and the $HL_{B,emp}$ estimate is therefore highly uncertain. Future HL_B QSARs should consider excluding acetazolamide from the training and testing sets. Other relatively common prediction errors by the QSARs are for *p,p′*-DDE, formaldehyde, 1,2-dichloroethene, and chloroethene; the latter three are small molecules and are not well suited for fragment-based QSARs.

Potential QSAR Applications. The general intent of the QSARs is to identify and examine structural features relating to *HL*s and to address data gaps for screening-level chemical assessments. QSAR predicted HL_Ts can be used to estimate the time required to approach steady-state and to calculate steady-state whole body concentrations (C_{ss}; mg/kg) based on intake rates (I; mg/kg/h), for example, $C_{ss} = I \times HL_T$. These calculations are approximations since they do not explicitly account for absorption and distribution processes. QSAR predicted HL_Bs can be used to estimate the time required to approach steady-state and to calculate steady-state whole body concentrations using 1-CoPK mass balance models that may or

may not include absorption and distribution processes.[6−8,17] Internal distribution coefficients can be used to obtain tissue and compartment specific concentrations from the 1-CoPK model if desirable.

The QSARs generally show similar statistics despite having many different molecular descriptors (fragments) (SI, Tables SI-6 and SI-8) and all of the QSARs may be useful in a weight of evidence or a consensus-based modeling approach, particularly in situations where uncertainty estimates from the models may be high. The QSARs can identify and prioritize chemicals with long *HL*s and high bioaccumulation and exposure potential. Chemicals outside the model domain for which the QSARs predict long *HL*s are indicative of chemicals with high bioaccumulation and exposure potential and such data gaps should be prioritized for in vitro (various mammalian species) and in vivo (rodent models) testing. For chemicals that do not contain any fragments in the QSARs, the HL_T and HL_B QSARs will give the respective intercept as the prediction and a warning that there is no fragment overlap with the training set.

Future Work. Variability in *HL*s is the result of several factors such as genetics, age, gender, general health, and enzyme induction and enzyme inhibition.[36] Recognizing that *HL*s are inherently variable and uncertain, we sought to develop screening-level QSARs for *HL*s in humans for high throughput screening-level bioaccumulation, exposure, and risk assessment. Despite the simplifying assumptions required and applied here for model parametrization, this study succeeded in developing validated QSARs for organic chemical *HL*s in humans based on in vivo data. These QSARs could be improved upon through revisions to the HL_B estimation model and its parametrization, more comprehensive empirical data evaluations, and different QSAR methods. For some chemicals K_{OW} and D_{OW} are not sufficient to characterize the chemical sorption capacity of the human body,[37,38] particularly for IOCs. For IOCs, descriptors that capture the effect of the charged atom could provide improved QSARs and new mechanistic insights in HL_B; however, as highlighted in this study the QSAR predictions for IOCs seem as good or better as the QSAR predictions for neutral organics. Complicating issues that may lead to errors in the reported *HL*s such as bioformation were not addressed here. Future efforts should also focus on obtaining biotransformation rates for a broader range of chemical classes and to examine similarities and differences in HL_B QSARs across species[19,20] and through a combination of in vitro and in vivo methods. Rates and pathways for chemical biotransformation are required to identify metabolites that may be more toxic than the parent chemical and the rate data and QSARs developed here could be integrated into existing QSARs and expert biotransformation pathway models for more comprehensive evaluations for the fate of the parent chemical and its metabolites in the body.[39−41]

■ ASSOCIATED CONTENT

Supporting Information

Details on (i) development of a 1-CoPK HL_B estimation model for mammals; (ii) parametrization of the HL_B estimation model for humans; (iii) corroboration and selection of HL_B estimates for QSAR; (iv) statistical summary of QSARs; and (v) details of two QSARs. This information is available free of charge via the Internet at http://pubs.acs.org/. QSARs are downloadable at www.arnotresearch.com.

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Notes

The authors declare no competing financial interest.

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