Environ. Sci. Technol. **2010,** *44,* 7711–7716

Influence of Taxonomic Relatedness and Chemical Mode of Action in Acute Interspecies Estimation Models for Aquatic Species

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Received May 13, 2010. Revised manuscript received August 6, 2010. Accepted August 12, 2010.

Ecological risks to aquatic organisms are typically assessed using acute toxicity data for relatively few species and with limited understanding of relative species sensitivity. We developed a comprehensive set of interspecies correlation estimation (ICE) models based on acute toxicity data for aquatic organisms and evaluated three key sources of model uncertainty: taxonomic relatedness, chemical mode of action (MOA), and model parameters. Models are least-squares regressions of acute toxicity of surrogate and predicted species. A total of 780 models were derived from acute values for 77 species of aquatic organisms and over 550 chemicals. Cross-validation of models showed that accurate model prediction was greatest for models with surrogate and predicted taxa within the same family (91% of predictions within 5-fold of measured values). Recursive partitioning provided user guidance for selection of robust models using model mean square error and taxonomic relatedness. Models built with a single MOA were more robust than models built using toxicity values with multiple MOAs, and improve predictions among species pairs with large taxonomic distance (e.g., within phylum). These results indicate that between-species toxicity extrapolation can be improved using MOA-based models for less related taxa pairs and for those specific MOAs.

Introduction

One of the greatest challenges in ecological risk assessment is to extrapolate across a broad range of species exposed to contaminants using limited toxicity data for commonly tested species (*1*). Generally, this requires extrapolation of toxicity data from a limited number of standard test species to a much larger number and diversity of species with unknown sensitivity. A traditional approach has been to apply generic safety factors to available test data. While used extensively, this approach contains large uncertainty because of limited knowledge of species sensitivity relationships. An alternative method that has been used determines a hazard concentration from a percentile (e.g., fifth) of a species sensitivity distribution (SSD) as a value that is representative of the more sensitive species (*2*). Application of SSDs is limited by their requirements for taxonomic diversity and chemical specific toxicity data for a number species. Where measured toxicity data are limited, additional methods are needed for populating SSDs and extrapolating chemical sensitivity relationships to ecological communities and untested taxa, such as endangered species.

Interspecies correlation estimation (ICE) models are log−linear least-squares regressions of the acute toxicity (EC/LC50) of chemicals measured in two species. An ICE model for a particular species-taxon pair can be used to estimate the toxicity to the predicted taxon using the known toxicity of that chemical in the surrogate species. Earlier development of ICE models has demonstrated that the species sensitivity relationship is a statistically viable approach for estimating acute toxicity (*3–6*) however, the validation and uncertainty of these models has been lacking for aquatic species. ICE models have been developed and validated for wildlife species (*7*) and their use in developing SSDs has been demonstrated for both wildlife (*8, 9*) and aquatic organisms (*10, 11*). Previously developed ICE models for both aquatic organisms and wildlife have been available on the U.S. Environmental Protection Agency (EPA) Web-based Interspecies Correlation Estimation (Web-ICE; http://www.epa.gov/ceampubl/fchain/webice/) application since 2007. This study aims to build on the previous work of ICE model development (*3–6, 12*) through uncertainty analyses that assess model accuracy relative to taxonomic relatedness, chemical mode of action (MOA), and model parameters.

We developed a suite of ICE models for a diversity of aquatic invertebrates, fish and some amphibians using strict standardization criteria for test methods and conditions (Tables S2 and S3, Supporting Information (SI)). Two critical factors of uncertainty in aquatic toxicity extrapolation, taxonomic relatedness and chemical MOA, were explored by assessing the effect on model uncertainty. Models were developed for 77 species using data compiled from diverse sources. Model uncertainty analyses determined (i) how closely to measured values ICE models predict toxicity, (ii) the relationship between ICE models and taxonomic relatedness of the surrogate and predicted taxa, (iii) which model parameters and attributes should be prioritized to select robust models a priori, and (iv) if single MOA ICE models improve toxicity estimations compared to models comprised of multiple MOAs.

Methods and Materials

Data Collection. The aquatic toxicity data set was comprised of 5487 acute EC/LC50 values for 180 species and 1258 chemicals. These data were compiled from the U.S. EPA ECOTOX (*13*), U.S. EPA Office of Pesticide Programs ecotoxicity database (accessed January 2007), U.S. EPA Office of Water Ambient Water Quality Criteria (*14*), U.S. EPA OPPT Pre-Manufacture Notification (PMN), U.S. EPA OPPT High Production Volume (HPV) Challenge Program, U.S. EPA Office of Research and Development data sources (e.g., ref *15*), Mayer and Ellersieck (*16*), and the open literature (see refs *17, 18*). All model data were consistent with standard acute toxicity test condition requirements outlined by the American Society for Testing and Materials (*19*, and earlier editions), and the U.S. EPA Office of Prevention, Pesticides, and Toxic Substances (*20*).

Data were subjected to rigorous quality assurance and standardization guidelines to ensure model relationships were reflective of intrinsic species sensitivity and contained minimal extraneous variation. Each record required a reported chemical name or structure with chemical active ingredient ≥90% and a reported end point of death (LC50)

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10.1021/es101630b © 2010 American Chemical Society
Published on Web 08/26/2010

or immobilization (EC50). Model data included 48 h EC/LC50 for daphnids, midges, and mosquitoes and 96 h EC/LC50 for fish and all other invertebrates. Open-ended toxicity values (i.e., > 100 μg/L or <100 μg/L) were excluded. Data were standardized by life stage by using only juveniles for fishes, amphibians, insects, molluscs, and decapods; all life stages were included for other groups (*18*).

All toxicity records for cadmium, chromium III, copper, lead, nickel, silver, zinc, pentachlorophenol, and ammonia were normalized according to Ambient Water Quality Criteria (*14*). Records that did not contain the water quality parameters necessary for normalization were excluded from the database. Large metal salts (molecular weight >200; e.g., copper naphthenate) were not normalized because of uncertainty in the relationship between their toxicity, hardness, and dissociation, and were treated as separate compounds.

Where multiple toxicity values were obtained for a species and chemical, the range of the minimum and maximum values for each chemical and species pair was calculated. These ranges, which represent interlaboratory variation of toxicity tests as well as identifying outliers, were within a factor of 2, 5, and 10 for 57, 86, and 94%, respectively. Where the range was greater than 10-fold, the original sources of suspected outliers were re-evaluated for data quality. If outliers could not be clearly identified, all data records for that chemical were removed for that species to eliminate potential data quality uncertainty (approximately 1.5% of species-chemical records). The geometric mean of toxicity values was determined where data were reported as a range or values were collected from multiple sources for a species and chemical.

Chemical Mode of Action (MOA) Assignments. A classification scheme for MOA for acute toxicity to fish and aquatic invertebrates was developed and applied to 707 organic and metallic compounds in the database. MOAs were first assigned using the U.S. EPA ASTER (assessment tools for the evaluation of risk; http://www.epa.gov/med/Prods_Pubs/aster.htm) MOA expert system. ASTER MOA assignments are based on the mode of acute toxicity in the fathead minnow and the structural fragments present in the chemical (*21, 22*). Nonpolar narcosis is the default MOA assigned by ASTER, but is only assigned if the structural characteristics of the chemical do not suggest a more specific MOA may be involved (*22*). ASTER MOA assignments were confirmed or revised based on professional judgment, including an assessment of chemical structure and available information on the mechanism of acute toxicity, therapeutic category, and pesticidal activity determined by review of Internet data sources, reports, and peer reviewed articles. Approximately 13% of ASTER-determined MOAs were superseded through this process.

Broad and specific MOA assignments were based on a review of the mode of action of action in fishes and supporting information on the mode of action in nontarget aquatic invertebrates. Broad MOA categories were developed by combining specific ASTER MOA categories (e.g., broad MOA narcosis is composed of multiple specific ASTER MOAs including nonpolar narcosis and polar narcosis). Specific MOA was a subcategory of broad MOA determined through best professional judgment or ASTER assignment (e.g., Broad MOA = AChE inhibition, Specific MOA = carbamate-mediated AChE inhibition). Each chemical was assigned to one of 11 broad and 21 specific modes of action (same MOA for fish and invertebrates), including uncertain/undetermined categories (SI Table S1).

Model Development and Validation. ICE Models were developed as model II least-squares regression in which variables are independent and subject to measurement error (*12*). An algorithm was written in S-plus (*23*) that paired every species with every other species having data available for at least three chemicals in common. For each species pair, a log−linear model calculated the ICE equation as $\text{Log}_{10}(\text{predicted taxa}) = a + b \times \text{Log}_{10}(\text{surrogate species})$, where a and b are the intercept and slope, respectively. Only significant models (p-value < 0.05) were used for further analyses.

Each model with a sample size of four or greater was validated using leave-one-out cross-validation. In this approach, each pair of acute values for surrogate and predicted species was systematically removed from the original model. A new model (submodel) was built with the remaining data and used to estimate the toxicity value of the removed predicted species from the respective surrogate species toxicity value. To compare the accuracy of a large number of diverse models, the N-fold difference of each estimated and actual value (nontransformed data) was used to determine the fit of the estimated toxicity value. The N-fold difference was determined as the maximum value of the estimated/actual or actual/estimated. Preliminary inspection of the ratio of estimated/actual was conducted to determine if ICE models were under- or overestimating toxicity. In general, half of estimated toxicity values were greater than the measured value and half were less, indicating that ICE models did not have a tendency for under or overestimation.

Model Uncertainty. The accuracy of model predictions was related to taxonomic relatedness using the results of the cross-validation and assigning each model a taxonomic distance value based on the taxonomy of the surrogate and predicted species. Distances were assigned such that surrogate and predicted species within the same genus = 1; family = 2; order = 3; class = 4; phylum = 5; kingdom = 6. Each cross-validated data point was assigned to a prediction category based on the N-fold difference of predicted and actual values. The categories were 5-fold (≤5-fold), 10-fold (>5-fold, ≤10-fold), 50-fold (>10-fold, ≤50-fold), and greater than 50-fold. The cross-validated data were compared among taxonomic distance and cross-validation categories using a Chi-square test for differences in probabilities (*24*).

Cross-validation results were used in a recursive partitioning approach (regression tree) to identify model attributes associated with high prediction certainty. The N-fold difference was dependent upon submodel attributes intercept, slope, R^2, p-value, degrees of freedom, mean square error, taxonomic distance, and the distance of the surrogate input value from the range of surrogate toxicity values used to develop the submodel. The latter variable was determined as the difference of the log-transformed input value from the average ± standard deviation of the log-transformed surrogate toxicity values. Data points cross-validated using submodels that were not significant at the $p < 0.05$ level and those with a fold difference of greater than 1000 were excluded from the analysis. The regression tree was built using JMP software (*25*).

Single MOA models were developed for all possible species pairs and broad and specific MOA categories. Within data subsets of each MOA, every species was paired with every other species for model development. All MOA models with four or greater data points were cross-validated using the leave-one-out approach described above. MOA-based models were compared to models developed using all chemical data (all data models) by pairing models by surrogate and predicted species and comparing model MSE with a sign test. This analysis tested the hypotheses that single MOA models are more robust, indicated by lower MSE, than models developed with multiple MOAs. Separate comparisons were conducted for all broad and specific MOAs where possible. All data models that originally contained only one MOA as a result of limited chemical diversity in the database for the surrogate and predicted species were not included in these

TABLE 1. Percentage of Cross-Validated Observations within Each Prediction Category Grouped by Closest Shared Taxon

shared taxonomic level	significant models (*N*)	percentage within prediction category			
		5-fold	10-fold	50-fold	>50-fold
genus	254	94	2	3	1
family	700	91	5	3	1
order	208	86	10	3	0
class	4432	80	9	8	3
phylum	764	61	14	17	8
kingdom	4556	56	15	19	10

comparisons because these models would be identical to the respective MOA-specific model.

The accuracy of toxicity prediction was compared between MOA-specific and all data models using the *N*-fold difference of data points removed from both models for the same species pair. For each taxonomic distance category, median fold difference of data points predicted by all data models was compared to that the respective MOA-specific models using Wilcoxon signed rank test.

Results

Model Uncertainty. There were 780 significant ICE models ($p < 0.05$) developed for 77 species from the database of all chemical toxicity records (SI Table S2). A total of 10 914 data points from 696 models were cross-validated. Model cross-validation showed a strong relationship between taxonomic distance and cross-validation prediction category (chi-square = 82.8, d.f. = 15, $p < 0.0001$). The percentage of data points in the 5-fold prediction category decreased with increasing taxonomic distance, whereas those in 50 and >50-fold difference category increased (Table 1). Overall, models built for two species in the same family predicted within 5 and 10-fold of the actual value for 91 and 96% of data points, respectively (Table 1). Information on all models, including statistics and parameters necessary for toxicity estimation (slope, intercept, degrees of freedom, number of chemicals in model, MSE, sum of squares) are available on the U.S. EPA Web-ICE application (http://www.epa.gov/ceampubl/fchain/webice/).

Regression Tree. The regression tree developed from modeling the *N*-fold difference against model attributes included 10 090 data points. The data were first partitioned using taxonomic distance, grouping submodels with taxonomic distances 1−4 separate from those of 5−6. For models with taxonomic distances 1−4, the data were next partitioned by the distance of the input value from the range of *x*-values used to develop the submodel. This split indicated that input values that were greater than 2 orders of magnitude than the mean + standard deviation have a mean fold difference of over 100. A third split of data that were within 2 orders of magnitude of the mean + deviation was performed using the submodel MSE and indicated that submodels with MSE < 0.22 predicted toxicity with an average fold difference of 4.40. For models with taxonomic distance of 5 and 6, models were next partitioned by those with MSE of less than and greater than 2.2, and then by the distance of the input value from the mean + deviation (Figure 1).

MOA-Based Models. MOA-based models were developed for 7 broad MOAs (494 models, 46 species) and 15 specific MOAs (424 models, 44 species). The diversity of models developed with specific MOAs were limited due to the reduced amount of data available within some MOAs (e.g., respiratory toxicity), as such comparisons with all data models were only made for six broad and eight specific MOAs (Table 2; SI Figure S1). Using MOA-specific data resulted in significant models for species pairs that did not have significant models developed using all chemical data. These new species pairs included a total of 32 broad and 22 specific MOA models. Conversely, ICE models built from all chemical data for 466 species pairs did not have any significant models using broad or specific MOA data subsets. Broad and specific MOA models are provided in SI Table S3. In general, single MOA models had lower MSE than all data models that have multiple and variable MOAs (SI Figure S1). The exceptions were the broad MOA metallic stress, and two specific MOAs: iono-regulatory toxicity and organophosphate AChE inhibitors (Table 2).

The improvement in prediction accuracy of MOA-based models was dependent on taxonomic relatedness and the type of MOA. Overall, the prediction accuracy of single MOA models did not improve for models of taxonomic distances 1−5 (within phylum). Despite lower MSE, the *N*-fold difference of cross-validated data points was not significantly different between all data models and single MOA models (Table 2, Figure 2). At taxonomic distance of 6 (within kingdom), MOA-based models were a significant improvement over all data models for many MOAs. The median fold difference of single MOA models was significantly lower than those of all data models for species pairs with taxonomic distance of six for the following MOAs: AChE inhibition, organophosphate AChE inhibition, narcosis, nonpolar narcosis, neurotoxicity, pyrethroid neurotoxicity, and reactivity.

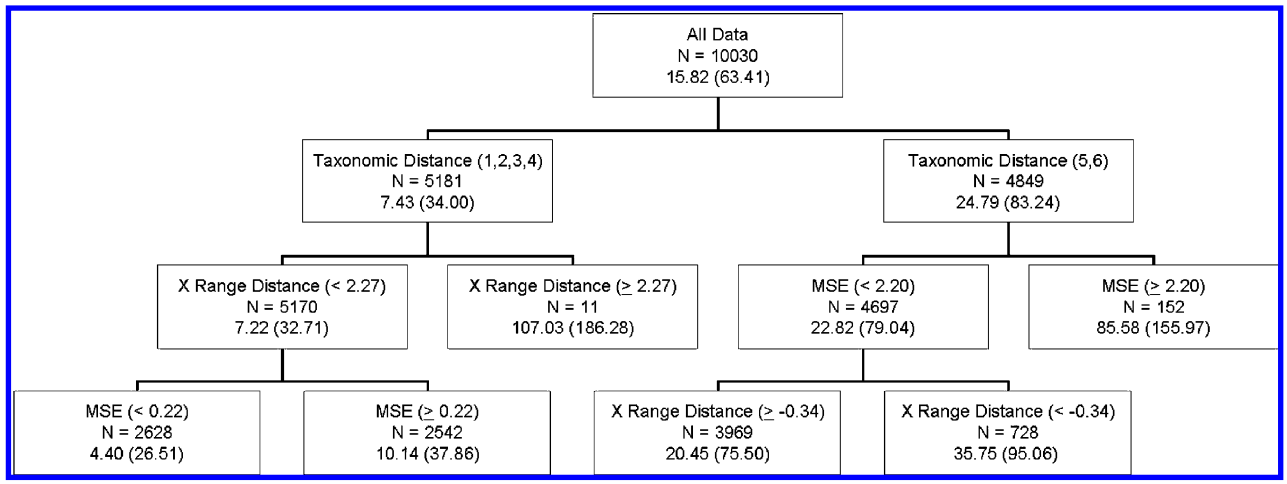

FIGURE 1. Regression tree of cross-validated data point modeled against model attributes. Each split identifies the model attribute by which submodels are partitioned. *N* is the number of submodels included in each split, followed by mean (standard deviation) of the fold-difference of cross-validated data points predicted by submodels within each partition.

TABLE 2. Comparison of Mean Square Error (MSE) for Models Built with All MOA data to Those Built With MOA-Specific Data[a]

mode of action[b]	number of models[c]	percent MSE lower in MOA models	*p*-value
AChE inhibition	164	59	0.0173
carbamate AChE inhibition	28	96	<0.0001
organophosphate AChE inhibition	82	55	0.2199
metallic stress	10	60	0.3770
iono-regulatory toxicity	10	80	0.0547
narcosis	92	95	<0.0001
polar narcosis	8	100	0.0039
ester narcosis	22	95	<0.0001
nonpolar narcosis	86	92	<0.0001
neurotoxicity	122	87	<0.0001
OC neurotoxicity	80	93	<0.0001
pyrethroid neurotoxicity	8	100	0.0039
reactivity	36	97	<0.0001
uncoupler/Inhibitor of oxidative phosphorylation	12	100	0.0002

[a] Models built from broad MOAs include data from all specific MOAs listed in Table 1. [b] The "number of models" is the total number of models that could be compared between each MOA and all chemical datasets. Only models that were significant when built with one mode of action were included. [c] The percent of lower MOA models is the percentage of models for which MSE was lower in the MOA model compared to the all data model.

Neurotoxicity also had significant lower median fold difference for models with taxonomic distance of four, which was driven by the specific MOA organochlorine neurotoxicity (Figure 2). Model prediction accuracy did not improve for other MOAs at any taxonomic distance.

Discussion

Interspecies toxicity extrapolation using regression analysis of acute effects has been explored in ecotoxicology for decades (*3–5, 26, 27*). Although earlier studies were based on limited species, chemicals, and chemical MOAs, they provided evidence that regression models could be used to predict acute toxicity (*3*) and were more robust for closely related species (*5*) and within chemical categories (*4*). This study developed ICE models with the most diverse species and chemical database to date and performed quantitative uncertainty analyses in relation to taxonomic distance, chemical MOA, and model parameters. These analyses provided guidance on model selection and use in ecological risk assessment. The models were derived using standardized acute toxicity values for aquatic invertebrates and fish. While the relevance of LC50 values to population protection is uncertain, acute toxicity data are the most comprehensive source of species sensitivity data for contaminants; both in terms of number of chemicals and species diversity. Acute toxicity values are an integral part of developing U.S. Ambient Water Quality Criteria, and are a foundation of developing screening values for ecological risk assessment internationally (*2*).

The taxonomic relatedness of the surrogate and predicted species was identified as a driving factor for prediction accuracy in all analyses. Using closely related species as surrogates for toxicity has been long recommended in risk assessment (*5*) and closely related species have been previously shown to produce more robust regression models (*4, 5, 7*). While Slooff (*5*) found higher correlation coefficients for species within the same taxonomic class, species and chemical diversity was limited and no distinct relationship was discernible. The relationship between toxicity and taxonomic relatedness has also been shown in other analyses of toxicological data. Baird and van den Brink (*28*) identified biological traits that accounted for 71% of the variability in sensitivity, correlating physiological similarities with species sensitivity. Raimondo et al. (*17*) showed that closely related species tended to group in similar quartiles of SSDs for some MOAs. The mechanisms underlying the importance of taxonomic relatedness in toxicity prediction likely involve species differences in toxicokinetics. For example, more closely related species may have greater similarities in uptake, disposition, and biotransformation.

Chemical MOA is a primary factor in species sensitivity and is a critical component of toxicity estimation using approaches such as QSAR (*29*), acute-to-chronic ratios (*30*) and the read-across approach (*31*). MOA assignments are one source of uncertainty in ICE models, in part due to limited knowledge of the mechanisms of acute toxicity in aquatic species, and the assignment of the same MOA to both fish and invertebrates. Additionally, some MOA assignments such as reactivity contained multiple specific mechanisms. These MOA categories were generalized/combined because of uncertainty in the specific mechanism of acute toxicity and requirements for adequate model sample sizes. Despite these uncertainties, MOA-specific ICE models improved interspecies toxicity extrapolation, particularly for unrelated taxa.

MOA-specific models were developed for over 50 species pairs that did not have significant sensitivity correlations using all chemical data, indicating a significant reduction in toxicity variability within MOA classes (SI Tables S2 and S3). While all analyses indicate that MOA specific models are more robust, the abundance and diversity of models is considerably less than models developed using all chemicals because of more limited data. The 466 significant species that did not have any correlations using MOA-specific data were primarily those with low sample sizes that did not contain enough data for MOA-specific models (87% with $N < 10$). Other species pairs that did not have significant MOA-specific models were those with high variability of all data (e.g., MSE > 1.0), which was preserved within MOA category.

While MOA-specific models generally improved toxicity estimation for unrelated species, their predictions for closely related species was not significantly better than all chemical data models. In these cases, the limited paired data of MOA-specific models relative to all data models likely increased uncertainty as the result of smaller sample sizes. For closely related species, accuracy for many all data models is similar to MOA-specific models. The mechanisms underlying the relationships between taxonomic relatedness and MOA may be attributed to species differences in both toxicokinetics and toxicodynamics. For example, closely related species may have greater similarity in sites of toxic action across the range of chemical MOA's within an all data model. In contrast, invertebrates and fish may have similar intrinsic sensitivity to nonspecific toxicants like narcotics, but differential responses to chemicals with more specific mechanisms such as acetylcholinesterase inhibition.

An important application of ICE models is the ability to populate SSDs with toxicity values for species without chemical specific data. Previous research has shown that ICE generated SSDs produce fifth percentile hazard levels similar to those derived with only measured values for both wildlife and aquatic species (*8, 9, 11*). The SSD is a widely applied approach that uses a distribution of toxicity for multiple species to determine a concentration that is considered nonlethal to most species (*32*) and are used in risk assessments throughout the United States and Europe (*33, 34*). While there is a general consensus that SSDs maybe built with 8−10 diverse species or genera (*33*), large sample

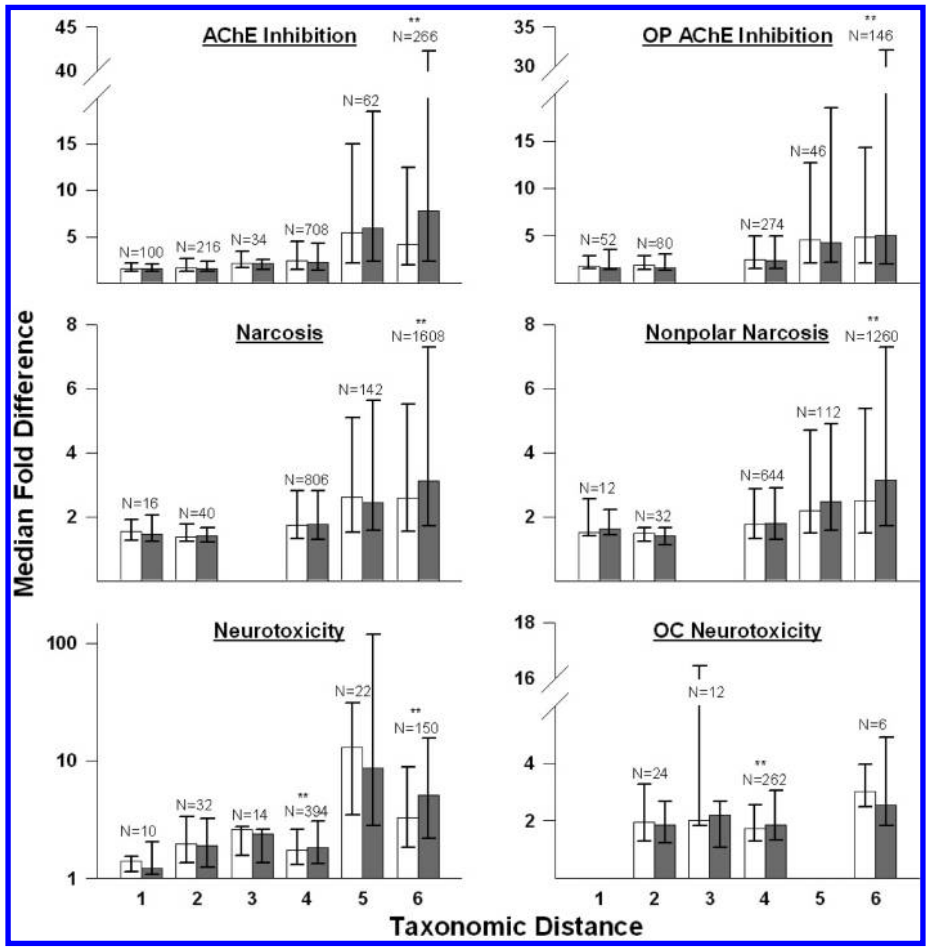

FIGURE 2. Comparison of prediction accuracy for example broad (left panels) and specific (right panels) MOAs. Taxonomic distances correspond to 1 = with genus, 2 = with family, 3 = within order, 4 = within class, 5 = within phylum, and 6 = with kingdom. Light bars represent models built with MOA-specific data, dark bars represent models built with all data.

sizes (up to 60) are recommended for greater confidence in hazard level estimation (*35, 8*). Toxicity estimated from ICE models can supplement SSD data sets to increase number and diversity of species within the distribution and reduce hazard level uncertainty.

Prior to inclusion of ICE estimated data into ecological risk assessment, model predictions should be evaluated for confidence. Models predictions should be evaluated based on close taxonomic distance, model MSE (<0.22), and the model domain of applicability. There remains some variability in predictions that was not explained by the uncertainty analyses, and further analysis of outliers will be conducted in future analyses. Our results provide the user a means by which to quantify the uncertainty surrounding ICE predictions, which should provide a greater level of confidence than alternative, arbitrarily selected safety factors (*36*).

The uncertainty analyses described in this study are based on cross-validation, which may not be considered a true validation of each model. However, cross-validation demonstrates the validity of the ICE modeling approach for predicting acute toxicity. Although models built with only three data points could not be validated using this approach, they are included in the Web-ICE suite of models based on the verification of the least-squares regression approach for predicting acute toxicity. Additionally, since the analyses described in this study are based on cross-validation, which verifies the approach rather than specific models, these conclusions should be preserved for updated ICE models developed with additional data.

ICE models predict acute toxicity, here defined as EC/LC50 values for 48 or 96 h of exposure under standardized conditions, to aquatic organisms with quantifiable confidence and known uncertainty. Taxonomic relatedness, model MSE, and the range of toxicity values used to develop models should be used to select models with high certainty. Model predictions may be used to supplement toxicity data used in ecological risk assessment through either direct toxicity estimation to species of concern or development of species sensitivity distributions. The ICE models developed from all chemical data discussed here are available in U.S. EPA Web-ICE version 3.1 (Release January 2010; http://www.epa.gov/ceampubl/fchain/webice/). The MOA-specific models will be added to Web-ICE following development of genus and family level models and should be available in 2011.

Acknowledgments

We thank Chris Russom (U.S. EPA, Mid-Continent), Brian Montague (U.S. EPA, Office of Pesticide Programs), Chris Ingersoll and Ning Wang (U.S. Geological Survey), Kimberly Salinas, Marion Marchetto, Nathan Lemoine, Nicole Allard, and Cheryl McGill (U.S. EPA, Gulf Ecology Division) and Lyle Burgoon (U.S. EPA Biostatistics and Bioinformatics Research Core), and Dave Mount (U.S. EPA, Mid-Continent Ecology Division). The information in this document has been funded wholly by the U.S. Environmental Protection Agency. It has been subjected to review by the National Health and Environmental Effects Research Laboratory and approved for publication. Approval does not signify that the contents reflect the views of the Agency, nor does mention of trade names or commercial products constitute endorsement or recommendation for use. This is contribution number 1391 from the Gulf Ecology Division.

Supporting Information Available

The number of records and chemicals for each broad and specific MOA are listed in Table S1. ICE models inclusive of all chemical data are available in Table S2. Model of Action-specific ICE models described in this study are available in Table S3. Graphical examples of models developed for all data compared to respective MOA-specific models are provided in Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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ES101630B