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High-Throughput Models for Exposure-Based Chemical Prioritization in the ExpoCast Project

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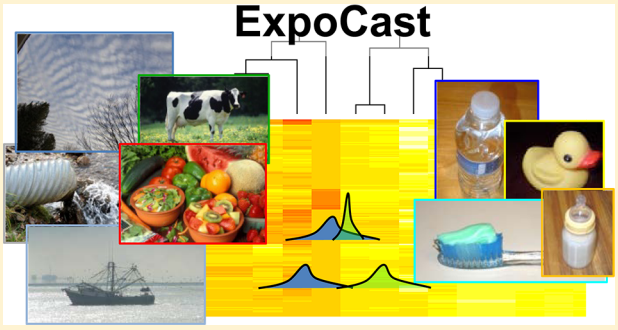
Supporting Information

ABSTRACT: The United States Environmental Protection Agency (U.S. EPA) must characterize potential risks to human health and the environment associated with manufacture and use of thousands of chemicals. High-throughput screening (HTS) for biological activity allows the ToxCast research program to prioritize chemical inventories for potential hazard. Similar capabilities for estimating exposure potential would support rapid risk-based prioritization for chemicals with limited information; here, we propose a framework for high-throughput exposure assessment. To demonstrate application, an analysis was conducted that predicts human exposure potential for chemicals and estimates uncertainty in these predictions by comparison to biomonitoring data. We evaluated 1936 chemicals using far-field mass balance human exposure models (USEtox and RAIDAR) and an indicator for indoor and/or consumer use. These predictions were compared to exposures inferred by Bayesian analysis from urine concentrations for 82 chemicals reported in the National Health and Nutrition Examination Survey (NHANES). Joint regression on all factors provided a calibrated consensus prediction, the variance of which serves as an empirical determination of uncertainty for prioritization on absolute exposure potential. Information on use was found to be most predictive; generally, chemicals above the limit of detection in NHANES had consumer/indoor use. Coupled with hazard HTS, exposure HTS can place risk earlier in decision processes. High-priority chemicals become targets for further data collection.



INTRODUCTION

The United States Environmental Protection Agency (U.S. EPA) must consider thousands of chemicals when devoting limited resources to assess risk to human populations and the environment.[1] Over 10 000 chemicals are currently in commercial use, of which only a fourth may have been adequately assessed for potential hazard.[1,2] The advent of high-throughput screening (HTS) approaches to characterize biological activity *in vitro*[3] motivated the development and implementation of U.S. EPA's ToxCast research program[4] as part of the federal Tox21 consortium.[5] These programs aim to advance a new, more efficient testing paradigm based on "predictive toxicology", whereby chemicals are prioritized for further testing and action based on *in vitro* activity profiles and potential disruption of key biological pathways.[6]

Recently, Judson et al.[7] described a high-throughput risk assessment approach: dose−response HTS *in vitro* toxicity data are used to identify potential biological targets for chemicals. *In vitro* methods are then employed to assess pharmacokinetics to estimate the human dose needed for each chemical to activate these targets *in vivo*.[8] Because risk is a function of both hazard and exposure, complementary rapid exposure screening tools must be developed to compare against these potential hazards identified by HTS.[9−13]

ExpoCast is a U.S. EPA initiative to develop the necessary approaches and tools for screening, evaluating, and classifying thousands of chemicals based on the potential for relevant human exposure.[14] As recognized in the National Research Council (NRC) report "*Exposure Science in the 21st Century: A*

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Vision and a Strategy", the "fundamental interdependence" of hazard and exposure data requires higher throughput exposure approaches.[11] For the majority of chemicals in commerce, the exposure data necessary for risk-based prioritization are lacking.[8,11] Furthermore, there is a need to assess potential exposure to chemicals before approval for commercial production. To meet this need, efficient exposure screening methods should be amenable to rapid implementation, be based on basic chemical properties, and provide quantitative estimates for hundreds to thousands of chemicals.

Physicochemical properties inherent to a given compound (e.g., octanol−water partition coefficients) and properties of those compounds in environmental media (e.g., degradation half-lives in soil) have been used to make high-throughput estimates of potential chemical exposure.[15−18] To date, these prioritizations have been on a relative rather than an absolute (i.e., mg kg^{-1} of body weight day^{-1}) scale. Environmental fate and transport and multimedia exposure models have been developed to model distribution and degradation in various environmental media. These mass balance models can be used to make predictions of human exposure based on "exposure factors", i.e., assumptions of human interactions with environmental media and derivation of food from the environment.[9,13] Minimally parametrized by predictions from chemical structure and release volumes, these models can be used to make high-throughput exposure estimates.[19,20] When other, near-field sources of exposure also exist, e.g., indoor emissions or direct contact with chemicals in products, this contribution to overall exposure can dominate far-field sources.[21] Careful consideration of the confidence in these predictions (i.e., uncertainty) is essential, and a comparison of model predictions to real world exposure data is highly desirable.[11]

However, monitoring environmental chemicals in the immediate vicinity of a population and identifying biomarkers of exposure is expensive and labor-intensive.[22,23] One program that contributes to this effort is the National Health and Nutrition Examination Survey (NHANES). NHANES is a program designed to assess the health and nutritional status of adults and children in the U.S. (http://www.cdc.gov/nchs/nhanes.htm). NHANES covers a few hundred of the thousands of environmental chemicals and potential metabolites for which data are needed[24] and would seem to provide a good test of high-throughput exposure models.

In this paper, we describe a framework for high-throughput exposure assessment. This ExpoCast exposure prioritization framework is structured such that (1) large numbers of chemicals can be rapidly and efficiently evaluated (i.e., high throughput), (2) models and data covering the diversity of routes of exposure can be incorporated and weighted as available and needed, and (3) consensus predictions of human (and ecological) exposure can be developed with an appropriate characterization of uncertainty. Here, we demonstrated the ExpoCast framework by applying two screening-level fate and transport models and an indicator of near-field use to predict human exposure potential for 1936 chemicals as a result of environmental release. A consensus exposure potential prediction model was then calibrated using NHANES biomonitoring. Results of this analysis provide insight into crucial determinants of exposure. The estimates of variance serve as an empirical determination of uncertainty, which has been used to prioritize 1936 chemicals with respect to exposure.

METHODS

General Approach. The ExpoCast exposure prioritization framework here is intended to be sufficiently flexible to incorporate new models as they become available. To rapidly screen a set of chemicals for exposure, we used linear regression to evaluate the predictive power of multiple exposure models by comparison to ground truth, e.g., exposures inferred from empirical data for a subset of the chemicals. Multivariate regression on the set of available high-throughput models provides regression coefficients for each of the models. The regression coefficients act as both weights for a single calibrated predictor for the ground truth data set and an assessment of model performance (a weight of zero indicates a lack of model predictivity for the data set in question). The variance of the ground truth about the calibrated predictor provided an empirical estimate of the uncertainty. The calibrated predictor and its uncertainty are then extrapolated to the remainder of the chemicals for which there were no ground truth data. Within this framework, new models can be evaluated for predictivity and ability to decrease uncertainty, while new data can be incorporated to better characterize model performance.

Table 1 includes the definitions of the acronyms and abbreviations used throughout the text.

Table 1. List of Acronyms and Abbreviations

AIC	Akaike Information Criterion
CDC	Centers for Disease Control and Prevention
CPRI	Crop Protection Research Institute
EPI Suite	U.S. EPA's Estimation Program Interface Suite
ExpoCast	U.S. EPA's Exposure foreCast prioritization research program
HTS	high-throughput screening
IUR	U.S. EPA's Inventory Update Reporting and Chemical Data Reporting list
K_{OW}	octanol−water partition coefficient
NHANES	National Health and Nutrition Examination Survey
NRC	National Research Council
PCA	principal components analysis
QSAR	quantitative structure−activity relationship
RAIDAR	Risk Assessment IDentification And Ranking model
ToxCast	U.S. EPA's Toxicity foreCast prioritization research program
U.S. EPA	United States Environmental Protection Agency
USEtox	United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model

Fate and Transport Models. The United Nations Environment Program and Society for Environmental Toxicology and Chemistry toxicity model (USETox), version 1.01,[13] and the Risk Assessment IDentification And Ranking model (RAIDAR), version 2.01,[9] multimedia mass balance models were used to predict quantities that could be related to exposure potential. Both models were necessarily capable of running in high-throughput mode and making quantitative exposure predictions.[20] On the basis of the compound-specific partitioning (e.g., fugacity) and degradation (i.e., media half-life) properties and the assumption of steady state (i.e., for a constant emission rate, sufficient time has passed that the concentration in each media is constant), the models predict chemical fate and distribution in representative environmental media (e.g., air, water, soil, sediment, and biota).

Having predicted the concentrations per unit emission in various environmental media, both models make additional assumptions to predict multiple human exposure pathways (i.e.,

inhalation, water ingestion, and various food ingestion) to calculate an overall population intake fraction (kilograms absorbed per kilograms emitted).[25] Similar quantities can be predicted for ecological end points. Further discussion of how the models were harmonized is available in Supplemental Methods 1 of the Supporting Information.

Chemical Selection. The ToxCast (phases I and II) chemical list includes over 1000 compounds, including industrial chemicals, pesticides, consumer product ingredients, and pharmaceuticals.[4] To this list were added roughly a thousand additional industrial and consumer use chemicals of general interest. Because RAIDAR and USEtox use separate, fundamentally different models to predict exposure to inorganic chemicals, the chemical set was restricted to organic chemicals to simplify the number of models under evaluation. The full list of chemicals considered is available in Supplemental Table 2 of the Supporting Information.

Model Parameterization. Model input parameters (see Supplemental Table 1 of the Supporting Information) were obtained primarily from Estimation Program Interface (EPI) Suite. In addition to estimation models, EPI Suite contains a database of experimentally obtained physicochemical properties that were used in place of quantitative structure−activity relationship (QSAR)-derived values when available.

Two sets of data were used to provide surrogates for chemical release to the environment. Information on the chemical production volume was obtained from the 2006 U.S. EPA Inventory Update Reporting and Chemical Data Reporting (IUR) (http://www.epa.gov/oppt/cdr/index.html) and used as a gross measure of the amount of compound released into the environment. Note that production volumes are provided in coarse bands (e.g., 1−10 million lb/year). For pesticides, Crop Protection Research Institute (CPRI) 2002 data on application levels by state and crop were aggregated, and resulting national application levels were used as a substitute for the overall production volume. Compounds that were not covered by CPRI and were not on the IUR were assumed to be produced between 0 and 25 thousand lb/year, the minimum requirement for being listed in the IUR.

Chemicals were identified as pesticides based on their presence on the CPRI list; all other chemicals were assumed to be industrial compounds. Two broad release profiles (pesticidal and industrial) were assumed and, depending upon the fate and transport model used, were characterized in slightly different manners. For pesticides, application was assumed to be equally to soil and air (50% soil and 50% air for RAIDAR and 50% continental agricultural soil and 50% continental air for USEtox), i.e., spraying. To assess environmental impact for chemicals handled under the Toxic Substances Control Act (TSCA), it is typical to assume either release from a smoke stack into the air or releases into water, because other releases onto land, water, or public treatment works are effectively releases into water.[17,26] Because the vast majority of the chemicals of interest here are those amenable to *in vitro* HTS [i.e., non-volatile and soluble in dimethyl sulfoxide (DMSO)], all chemicals other than pesticides were assumed to largely be released to water (80% water, 10% soil, and 10% air) for RAIDAR and continental freshwater (75% continental freshwater and 5% to each of continental natural soil, agricultural soil, air, and seawater and urban air) for USEtox.[17] The release profiles used for each compound are presented in Supplemental Table 6 of the Supporting Information.

Chemical Use Information. Chemical use information was estimated from the ACToR database (http://www.epa.gov/actor/). The sources for various chemical data were primarily federal, state, and international regulatory listings for chemicals falling into specific classes. These data were assigned to various use categories. Chemicals with data from multiple sources were assigned to multiple categories. Filters were applied to eliminate inappropriate assignments. The number of times that a chemical appeared on lists assigned to each category was tabulated; a threshold (3) was used to make a Boolean classification of whether a chemical was in a category. Chemicals above the threshold were automatically assigned to the category; chemicals with no hits were automatically not assigned to the category; and chemicals with fewer hits than the threshold were manually curated. Five categories, personal care products, consumer use, fragrance, pharmaceutical, and food additive, were aggregated into a single "near-field" indicator variable (i.e., having a value of 1 if some near-field use exists and 0 otherwise).

Biomonitoring Data. The National Health and Nutrition Examination Survey (NHANES) is conducted by the Centers for Disease Control and Prevention (CDC) at multiple locations throughout the United States. NHANES provides a report on the urine concentrations of many chemicals. For this analysis, the total adult (age 20 and older) population was used. We note that, in some cases, NHANES data have been recalled and that our analysis includes only those data that the CDC supports as of May 2013.[27]

A reverse pharmacokinetics approach[28,29] was used to infer exposure from NHANES biomonitoring data for creatinine-adjusted urine concentrations. Assumptions similar to those by Mage et al.[28] were made, chiefly that the individuals were at steady state as a result of a constant rate of exposure. An average daily creatinine excretion of 122.6 mg/dL,[27] the body weight measured by NHANES,[27] and an average daily urine volume of 1.4 L[30] were used along with a mapping (see Supplemental Figures 1 and 7 of the Supporting Information) derived from the NHANES reports between parent and metabolite compounds (including the relative molecular weights) to convert the urine concentration to an exposure in units of mg kg^{-1} day^{-1}. Further discussion of the pharmacokinetic approach is available in Supplemental Methods 2 of the Supporting Information.

Statistical Analysis. The statistical analysis was carried out in three stages: (1) Using Bayesian methods (Markov Chain Monte Carlo via JAGS, version 3.1.0[31]), log geometric mean exposures to parent compounds were estimated from population quantiles of distributions of product concentrations in NHANES urine samples. To use estimates that fell below the limit of detection, it was assumed that the population distribution of compounds in urine was log-normal. This assumption was checked by comparing geometric mean population exposures computed this way to the geometric means provided in the NHANES reports. Errors were smaller than 20%. Stoichiometric relationships (see Supplemental Table 7 of the Supporting Information) between parent and urine product (e.g., metabolite) were either assumed to be known fixed values or were themselves estimated, preserving mass balance. (2) A null model (one value for all chemicals) and 22 nested linear models were examined for fitness. The 22 models related log geometric mean population exposures to predictors consisting of subsets of log RAIDAR and USEtox unit emissions, log production volumes, near-field contrast, and

the interaction effects of near-field contrast and the log unit emission estimates and log production volume. Each model was fit to repeated samples of the posterior distribution of the log geometric mean inferred parent exposure concentrations from stage 1. Production volumes were drawn from a distribution reflecting the uncertainty for that chemical (e.g., 1−10 million lb/year). Models were selected by comparing mean Akaike Information Criterion (AIC)[32] values, and the model selection was checked using 10-fold cross-validation. (3) The model selected from stage 2 was fit to the NHANES samples using Bayesian methods, combining the estimation process described in stage 1 with the model relating log exposure to predictors identified in stage 2. Predictive intervals for exposure estimates were computed as quantiles of the resulting posterior predictive distributions.

Full details of the statistical analysis are provided in Supplemental Methods 3 of the Supporting Information.

RESULTS

Data Availability. The breakdown of available chemical-specific data is illustrated in Figure 1. Of the 2127 chemicals initially considered (see Supplemental Table 2 of the Supporting Information), the physicochemical data required for model parametrization (see Supplemental Table 1 of the Supporting Information) could be found or calculated for only 1950 of these chemicals (leaving 167 without complete sets of model parameters). Experimental data were used for only six of the model parameters (see Supplemental Table 1 of the Supporting Information), and only 4.8% of the chemicals had data for all six. EPI Suite's QSARs were used if SMILES descriptions were available, and the QSARs did not fail for that structure. All parameter values are given in Supplemental Table 3 of the Supporting Information.

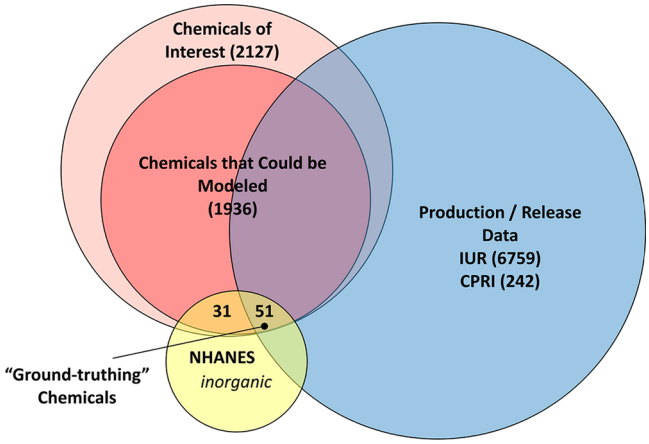

Figure 1. There is limited exposure data for actually evaluating high-throughput exposure models. From an initial list of 2127 chemicals, including all ToxCast to date, 1936 chemicals had sufficient physicochemical properties available to parametrize fate and transport models and use data. Production/release data were available for 975 of these chemicals. Of 82 parent chemical exposures that can be inferred from the NHANES data set, 31 of these chemicals had to be assumed to be produced at less than 25 000 lbs/year because they were not on the IUR or CPRI lists.

As identified by principal components analysis (PCA), the half-lives in environmental media and the bioconcentration factor, which is a measure of the concentration in fish relative to surrounding water, most distinguished one compound from another (see Supplemental Figure 2 of the Supporting Information). While 50.7% of the chemicals had measured K_{OW} and 54.3% had measured water solubility, half-lives were determined only from QSARs calibrated to the results of a 17 member expert panel that categorized 200 chemicals into semi-quantitative time categories (hours, days, weeks, months, and longer than months).[33]

With the necessary transformations for the model inputs to USEtox and RAIDAR (given in Supplemental Tables 4 and 5 of the Supporting Information, respectively) and the assumed release profiles (see Supplemental Table 6 of the Supporting Information), compound-specific exposure model predictions could be made (see Supplemental Table 14 of the Supporting Information) for 1950 chemicals. Of the 1950 chemicals for which EPI Suite did not fail, a further 14 chemicals had no use data, leaving 1936 chemicals for which exposure predictions could be made.

The IUR provided production volumes for 6759 chemicals, and the CPRI provided usage for 153 pesticides, allowing for release estimates for a total of 6907 unique compounds, of which 975 overlapped with the 1936 chemicals. Most restrictive was the NHANES biomonitoring data, which covered only 96 of the 1936 chemicals, 14 of which were removed for having no indication of production/release (e.g., metabolites only; see Supplemental Table 8 of the Supporting Information) or for being inorganic (arsenic), leaving 82 ground truth chemicals.

Environmental Model Predictions. Figure 2 clusters chemicals based on USEtox and RAIDAR predictions of partitioning into various environmental media. The continental USEtox media predictions and the RAIDAR predictions are similar (USEtox also predicts the global concentrations resulting from the same continental release).

Using the environmental partitioning results from Figure 2, both RAIDAR and USEtox make assumptions about human exposure pathways that allow for human exposure metrics to be calculated, including an overall population intake in units of kilograms exposed to the population per kilograms emitted (i.e., intake fraction). Figure 3 shows general agreement between the predicted intake fractions for the two models, except for select chemicals with relatively low hydrophobicity ($\log K_{OW} < 1$). This discrepancy is largely due to differences in the way that the models simulate chemical accumulation in vegetation as a function of whether non-hydrophobic compounds will eventually reach the plants at steady state.

Plotted with triangles in Figure 3 are compounds that would be considered to be "likely bioaccumulators" [$\log K_{OW} > 4.5$ and a bioaccumulation factor (BAF) > 1000].[18] Most likely bioaccumulators are predicted to have high intake fractions.

The domain of applicability of the NHANES chemicals used for ground truthing can be in part assessed by the convex hull of the intake for the NHANES chemicals (shown by a polygon in Figure 3). Although it does not completely cover the range of values predicted by USEtox and RAIDAR, the 82 NHANES chemicals do cover a wide region of predicted intake fractions. Chemicals with high intake fractions appear to be slightly underrepresented by NHANES, with only 4.2% of the NHANES chemicals having intake fractions greater than 10^{-3} for both models, while this occurs for ~12% of the overall chemicals.

Generally, the chemical properties of (see Supplemental Figure 2 of the Supporting Information) and chemical-specific model predictions and production volume data for (Figure 3 and see Supplemental Figures 3 and 4 of the Supporting

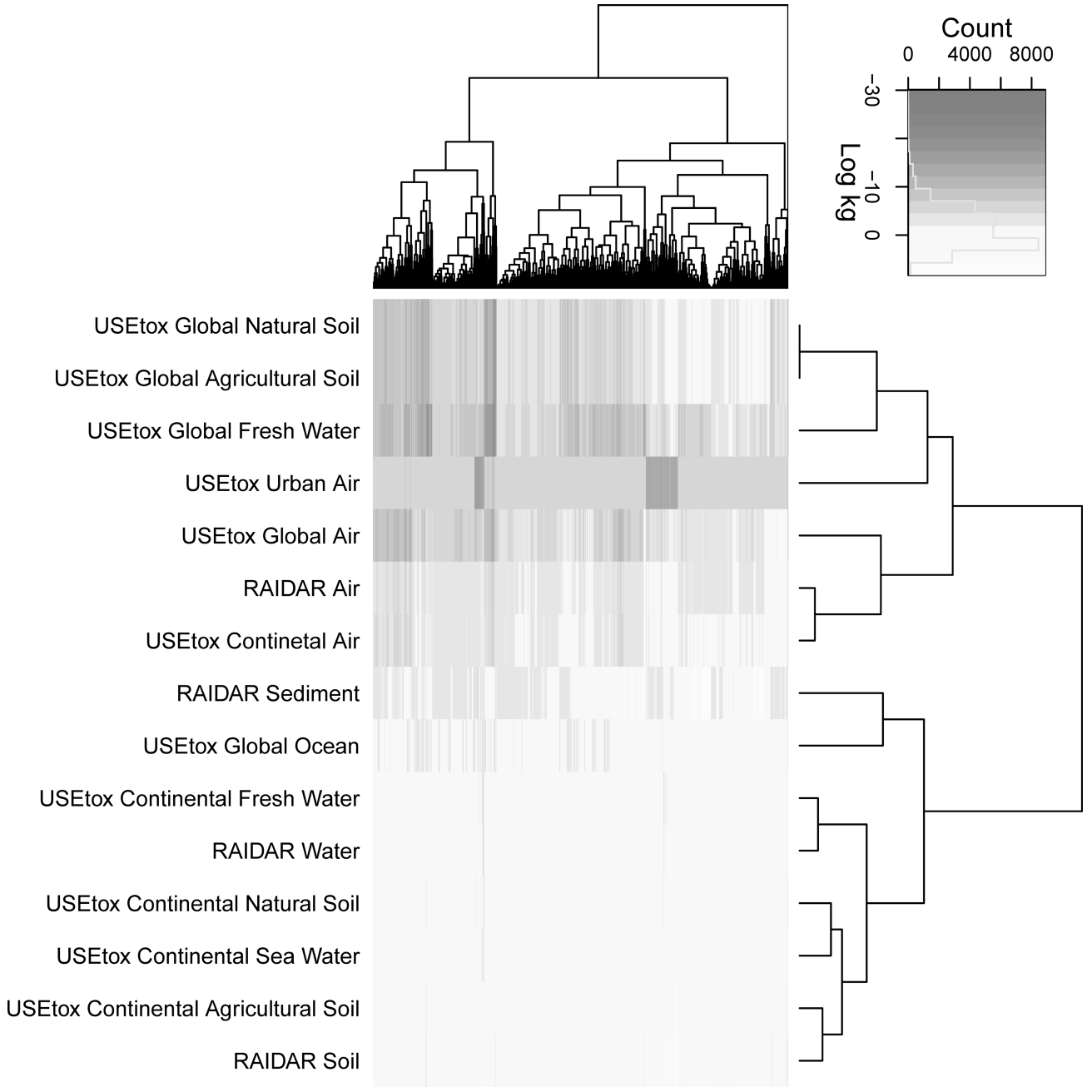

Figure 2. Far-field models predict the distribution of chemicals into environmental media, from which human exposure can be inferred via exposure factors. The current models make predictions for 1936 chemicals, which have been clustered here on the basis of the amount (kg) of compound predicted to be present in each environmental medium as the result of a unit emission (1 kg/day). The two-way clustering used Euclidean distance of the logarithm of the partition fraction and complete linkage (pair with maximum distance used to compare clusters).

Information) the 1854 chemicals without NHANES data appear to be within the range of the 82 chemicals with NHANES data, indicating that most chemicals may be within the domain of applicability of the empirical calibration.

Evaluation of Predicted Exposure via Model Calibration. The ultimate goal of this research was to develop a framework to determine the effectiveness of high-throughput exposure models for ground-truth chemicals and apply the resulting calibration to other chemicals with no monitoring data. On the basis of the analysis of the 82 parent chemical exposures inferred from NHANES, a calibrated model with intercept and regression coefficients for the unit USEtox and RAIDAR predictions for the near-field chemicals only and a separate intercept only for the far-field chemicals (coefficients given in Supplemental Table 11 of the Supporting Information) were selected from among the five most parsimonious models. This model was selected for including both RAIDAR and USEtox predictions and having a low AIC, which is a statistical measure of model parsimony (see Supplemental Table 9 of the Supporting Information).[32] The AIC value for this model was found to be stable with respect to 10-fold cross-validation (see Supplemental Figure 6 of the Supporting Information). A model excluding USEtox (coefficients given in Supplemental Table 12 of the Supporting Information) was slightly more parsimonious, but the difference was not statistically significant.

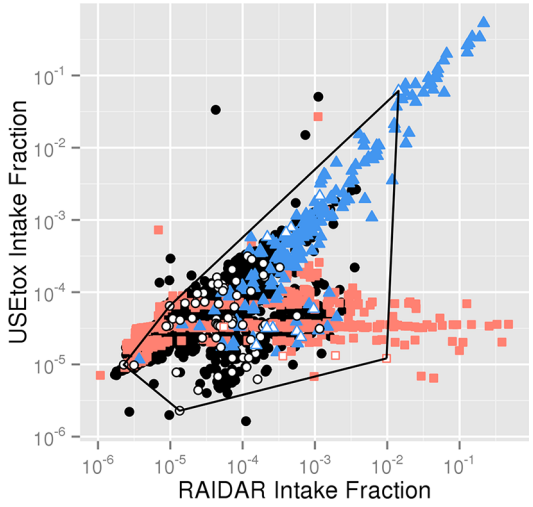

Figure 3. USEtox and RAIDAR predict intake fraction (kilograms exposed to the population per kilograms emitted) via exposure factors that translate predicted environmental media concentrations into human exposure metrics. Of particular interest are putative bioaccumulators (indicated by triangles), compounds with log K_{OW} < 1 (indicated by squares), and the NHANES chemicals (indicated by open symbols). A convex hull of the NHANES chemicals indicates reasonable coverage of the predicted exposure space by those chemicals. Approximately 88% of the chemicals are predicted by both models to have intake fractions below 10^{-3}.

Near-field use was the single most predictive chemical aspect (p value of 0.01 without any other factors). Those chemicals flagged as having indoor/consumer use yield significantly greater NHANES-inferred exposures on average than for the chemicals that were not flagged. Neither USEtox nor RAIDAR total predictions (i.e., predicted unit emission multiplied by production volume) alone are significantly associated with the 82 NHANES chemicals (p values of 0.077 and 0.194, respectively; see Supplemental Table 10 of the Supporting Information). Generally, chemicals above the limit of detection in NHANES had consumer/indoor use, while those with only the far-field sources for which the fate and transport models were designed were below the limit of detection. The 10-fold cross-validation diagnostics did not indicate that the correlations were driven by specific chemicals (see Supplemental Figures 5 and 6 of the Supporting Information).

The ability of this method to predict potential exposure is evaluated in Figure 4, where the empirically calibrated, optimal predictor (see Supplemental Table 11 of the Supporting Information) based on RAIDAR, USEtox, and the near-field indicator is compared to the geometric mean U.S. population exposures inferred from NHANES urine metabolites (see Supplemental Table 13 of the Supporting Information). Despite the large scatter, the joint model predictor appears to be without obvious bias (i.e., does not under-/overpredict). Taking no correlation as a null hypothesis, the p value for the calibrated predictor is 0.017.

The relative certainty in the exposures inferred by reverse toxicokinetics (y axis) is indicated by the vertical confidence

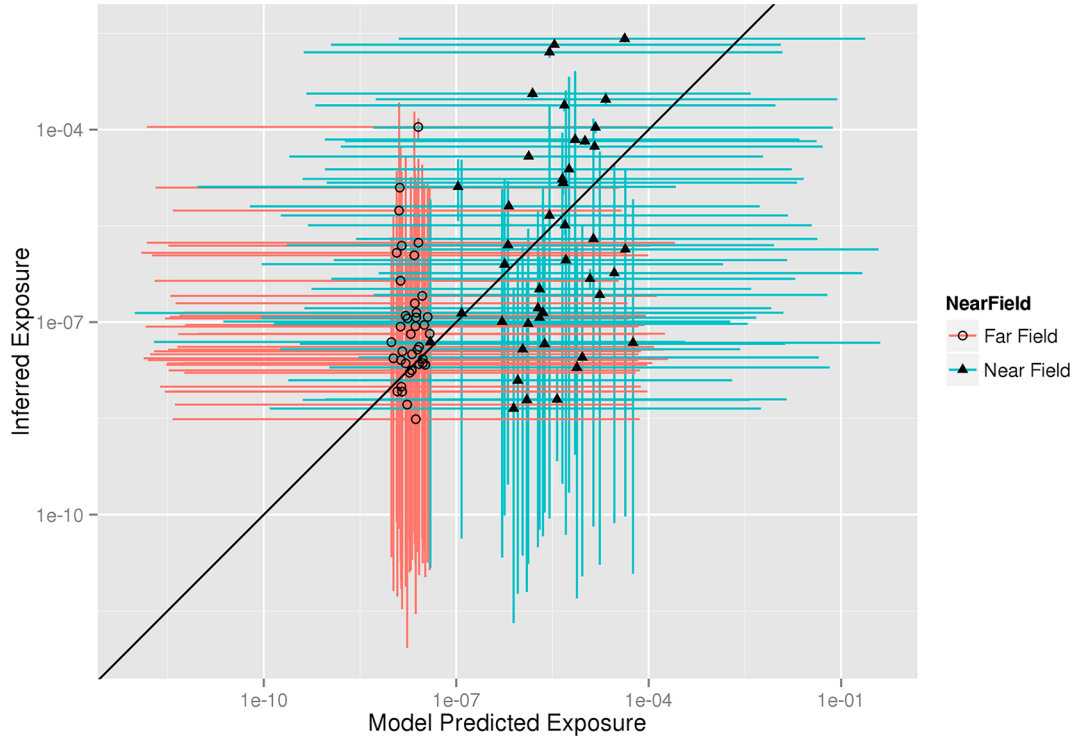

Figure 4. Correlation of inferred exposures and the consensus model indicates predictive power (p value of 0.017). Exposures inferred from NHANES biomonitoring data were linearly regressed on the unit emission predictions of RAIDAR, USEtox, and a near-field use indicator variable to create a calibrated predictor for predicted exposure (mg kg^{-1} day^{-1}). The solid line indicates the 1:1 line (perfect predictor). Bayesian analysis was used to distribute urine products using mass balance, giving the 95% confidence intervals (light lines) and medians (solid triangles for compounds with near-field use and open circles for far-field use only). The regression coefficients are available in Supplemental Table 11 of the Supporting Information. The uncertainty of the inferred exposures (width of the vertical confidence interval) is strongly dependent upon the number of general population quantiles with concentrations below the limit of detection in NHANES.

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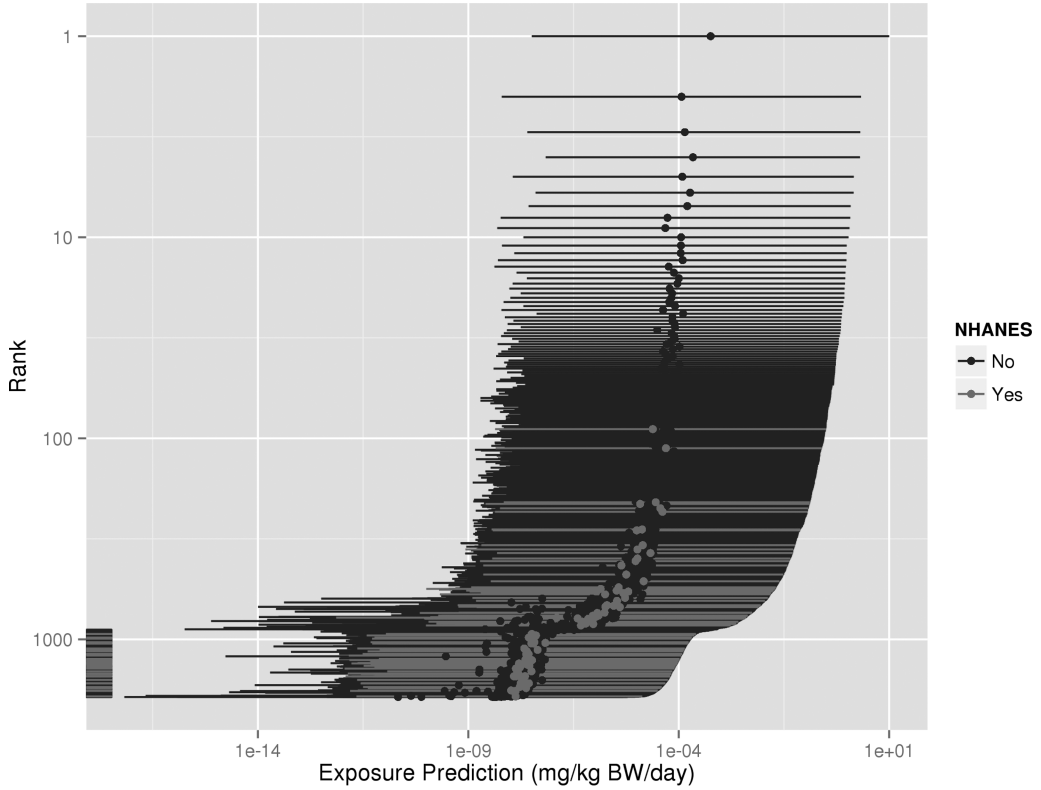

Figure 5. Predicted human exposure (mg kg^{-1} day^{-1}) for 1936 chemicals found by empirically calibrating high-throughput model predictions to be consistent with exposures inferred from NHANES. The uncertainty in each prediction is indicated by the horizontal 95% confidence interval. NHANES chemicals used for the calibration are indicated by the lighter confidence interval bars. The black tick marks on the left hand side indicate compounds with only far-field uses.

interval in Figure 4. Those chemicals with a large uncertainty in the inferred exposure estimate likely have complex parent exposure−urine product relationships (e.g., the metabolite dimethylphosphate can result from exposure to 17 different parent organophosphate pesticides; see Supplemental Figure 1 of the Supporting Information) or were below the limit of detection. Note that the vertical placement of plot symbols in Figure 4 indicates the median-inferred exposure; for chemicals where many or all NHANES urine products were below the limit of detection, the median is no more likely to be the true exposure value than any other value within the vertical confidence interval.

Given the predictions of the empirically calibrated consensus model, ranking on the basis of predicted exposure was conducted for all 1936 chemicals based on the upper limit of the 95% confidence interval from the empirical calibration to the NHANES data. However, as shown in Figure 5, the large uncertainty associated with the far-field models and coarse near-field indicator predictor, indicated by the horizontal error bars at each plot point, should lead to skepticism of specific predicted values. Despite this uncertainty as to the specific exposure level within the confidence interval, Figure 5 indicates that, for all but the top 100 chemicals, there is 95% confidence that exposures will be less than 0.29 mg kg^{-1} of body weight day^{-1}. For the bottom 1000 chemicals, there is 95% confidence that exposures are less than 0.27 μg kg^{-1} of body weight day^{-1}.

DISCUSSION

This study demonstrated the feasibility of HTS exposure profiling for quantitative predictions of exposure potential for 1936 chemicals. Linear regression on exposures inferred from NHANES data allowed for evaluation of correlation (model predictive ability) and an empirical calibration such that exposures consistent with NHANES data were predicted for all chemicals. More importantly, the variance about this calibrated predictor provided an empirical quantification of uncertainty. Finally, this work has identified large data needs to provide either initial or improved prediction of environmental chemical exposure. Of special importance is the need to better model and reflect variations in near-field sources of exposure.

Both environmental half-lives and physicochemical properties have long been considered drivers of environmental fate and potential exposure.[15−18] However, positive correlation between exposure prioritizations based on these properties and other measures of exposure have been elusive.[15,34] Thus, the predictive ability of the selected model indicates value gained by this modeling approach.

Exposures are inferred via reverse toxicokinetics from the NHANES data set for 82 chemicals, and the inferences for these chemicals alone allow for model evaluation. The properties of (see Supplemental Figure 2 of the Supporting Information) and predictions for (Figure 3 and see Supplemental Figures 3 and 4 of the Supporting Information) these chemicals are roughly representative of the 1936 chemicals. These inferred exposures provide a data set for comparison to exposure model predictions and allow for calibration and an empirical determination of predictive uncertainty. Some of the inferred exposures have large uncertainty themselves, likely because of complex parent exposure−urine product relationships or urine concentrations that were below the limit of detection.

Exposure inference from the NHANES data was conducted under the assumption of steady-state conditions. Although this assumption was necessary for the current analysis, it is unlikely to be true for most chemicals, particularly those that are rapidly metabolized. As medium- to high-throughput pharmacokinetic data becomes available (e.g., the study by Wetmore et al.[8]), it may eventually be possible to characterize the confidence in these inferences with respect to the drivers of variability (e.g., exposure frequency, duration, and chemical metabolism/excretion half-life). As finer grained chemical use information becomes available, it might be used jointly with basic pharmacokinetic data to eliminate the need for the steady-state assumption altogether. At this time, the steady-state assumption appears to be the best available for high-throughput exposure methods and is a contributor to the overall uncertainty estimated here.

Given the observed importance of near-field relative to far-field releases, future efforts for human health assessment should focus less on refinement of far-field models and, rather, emphasize additional exposure data and models that characterize proximate sources/uses. In the NHANES data, chemicals with near-field sources are generally above the limit of detection, whereas those with far-field only sources were generally below the limit of detection, providing only minimal information for evaluating far-field exposure routes. Most of the NHANES compounds with products in urine above the limit of detection have significant and diverse use in the home that could produce near-field releases. For these chemicals, near-field sources are a much more significant driver than the diffuse, continent-wide sources of far-field models.[35]

Many proposed near-field models are sensitive to the same physicochemical properties as fate and transport models and would benefit from improved data.[36,37] Measured and predicted data from EPI Suite were not evaluated for quality. Any uncertainties and errors are distinct from those of the evaluated models but contribute to the empirically estimated uncertainty. Further, EPI Suite could not predict all necessary properties for 167 of the chemicals initially considered. HTS for physicochemical properties[38] could reduce or eliminate the need for some QSARs to predict these properties while allowing other QSAR methods to expand into new regions of chemical space. Assays amenable to HTS exist for physicochemical properties[38] as well as for half-lives in environmental media.[39] *In vitro* assays to estimate biotransformation half-lives may be especially valuable.[34] The rate-limiting step in half-life assays is typically the chemical-specific analytical chemistry methods, which are available for many ToxCast chemicals.[8]

Additional data are also needed to better characterize the release of compounds into the environment. A determination of whether a chemical was a "pesticide" was solely based on whether or not the chemical was on a list compiled by the CPRI. This list is not complete, and points to the need for more reliable sources of information for large numbers of chemicals. For those chemicals covered by CPRI, data on the kilograms applied agriculturally were available. For all other chemicals, production volume data were used as a crude surrogate for actual chemical release. This simplification is a key issue for models such as USEtox and RAIDAR; the volume released into the environment is a multiplicative factor, and results are extremely sensitive to errors in the emission characterization.[40] Although U.S. EPA IUR production volume category data are available for many chemicals, these categories can span an order of magnitude and are not directly linked to intended use, e.g., environmental versus indoor releases. However, as shown in Figure 1, many NHANES chemicals were produced at levels less than 25 thousand lb/year and their presence in the urine of the general population was driven by near-field use rather than these traditional metrics of production and far-field environmental release.

Finally, expanded monitoring data are needed to better characterize actual exposures. For the majority of chemicals, where resources, such as NHANES data, are not available, new more flexible approaches are needed to quantify population-level chemical exposures. HTS techniques are becoming available that can simultaneously screen for thousands of xenobiotic chemicals as well as endogenous markers of biological response and exposure in serum.[41]

Here, we demonstrated a method for rapid exposure-based prioritization of chemicals using minimal information. However, characterizing risk for large numbers of chemicals requires reliable information regarding both hazard and exposure, with appropriate uncertainty and variability. Ultimately, predicting distributions of potential exposures in a high-throughput manner must complement the high-throughput hazard assessment work that is underway.[7,8] In the study by Wetmore et al.,[8] the vast majority of human oral equivalent (mg kg^{-1} day^{-1}) doses needed to cause ToxCast bioactivities were in excess of 10^{-4} mg kg^{-1} day^{-1}, while in Figure 5, we find that, even with large estimated uncertainty, the upper limit of the 95% confidence intervals for the bottom 668 chemicals are below this level. At this initial stage, however, our results are primarily appropriate for identifying areas of future research vital to providing sufficient high-throughput exposure assessment.

Future work will also be needed to address population variability. Here, we have calibrated to the NHANES total population numbers; however, chemical data are available for specific demographics (e.g., children aged 6−11), and calibrations to these demographics may identify drivers of exposure that vary among populations. The exposure scenarios of the models applied here as well as future models can be customized to represent demographics beyond the general population (e.g., highly exposed and sensitive subpopulations).

The ExpoCast exposure prioritization framework is designed to apply to large numbers of chemicals, to incorporate new models as they become available, to weight model components appropriately, and to make predictions of human (and in due course ecological) exposure, all with an appropriate characterization of uncertainty. This framework meets the mandate of the NRC for an objective, standardized, and transparent approach to high-throughput exposure modeling.[11]

As new models are incorporated into the ExpoCast framework, the results reported here will serve as a baseline. There is a clear need to develop screening tools for near-field human exposures. We hope that the value of future exposure prioritization work can now be quantitatively demonstrated by reducing the large uncertainties currently associated with predicting human exposure to environmental chemicals.

■ ASSOCIATED CONTENT

Supporting Information

Further discussion of the far-field models used, the use of biomonitoring data for exposure inference, and the Bayesian statistical methodology used and all chemical descriptors, model results, and statistical analyses. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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