SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

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Abstract

United States Environmental Protection Agency (USEPA) researchers are developing a strategy for high-throughput (HT) exposure-based prioritization of chemicals under the ExpoCast program. These novel modeling approaches for evaluating chemicals based on their potential for biologically-relevant human exposures will inform toxicity testing and prioritization for chemical risk assessment. Based on probabilistic methods and algorithms developed for The Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Chemicals (SHEDS-MM), a new mechanistic modeling approach has been developed to accommodate high-throughput (HT) assessment of exposure potential. In this SHEDS-HT model, the residential and dietary modules of SHEDS-MM have been operationally modified to reduce the user burden, input data demands, and run times of the higher-tier model, while maintaining critical features and inputs that influence exposure. The model has been implemented in R; the modeling framework links chemicals to consumer product categories or food groups (and thus exposure scenarios) to predict HT exposures and intake doses. Initially, SHEDS-HT has been applied to 2507 organic chemicals associated with consumer products and agricultural pesticides. These evaluations employ data from recent USEPA efforts to characterize usage (prevalence, frequency, and magnitude), chemical composition, and exposure scenarios for a wide range of consumer products. In modeling indirect exposures from near-field sources, SHEDS-HT employs a fugacity-based module to estimate concentrations in indoor environmental media. The concentration estimates, along with relevant exposure factors and human activity data, are then used by the model to rapidly generate probabilistic population distributions of near-field indirect exposures via dermal, non-dietary ingestion, and inhalation pathways. Pathway-specific estimates of near-field direct exposures from consumer products are also modeled. Population dietary exposures for a variety of chemicals found

in foods are combined with the corresponding chemical-specific near-field exposure predictions to produce aggregate population exposure estimates. The estimated intake dose rates (mg/kg/day) for the 2507 chemical case-study spanned 13 orders of magnitude. SHEDS-HT successfully reproduced the pathway-specific exposure results of the higher-tier SHEDS-MM for a case-study pesticide, and produced median intake doses significantly correlated ($p<0.0001$, $R^2=0.39$) with medians inferred using biomonitoring data for 39 chemicals from the National Health and Nutrition Examination Survey (NHANES). Based on the favorable performance of SHEDS-HT with respect to these initial evaluations, we believe this new tool will be useful for HT prediction of chemical exposure potential.

INTRODUCTION

The timely assessment of the risks posed to public health by tens of thousands of existing and emerging commercial chemicals is a critical challenge facing the United States Environmental Protection Agency (USEPA) and regulatory bodies worldwide.[1,2] The pace of conducting risk assessments is limited by the pace at which defensible and fit-for-purpose information can be generated on anticipated biological effects and on expected human exposures. Due to significant data gaps in both hazard and exposure information for risk-based prioritization of chemicals, there is a need to develop, apply, and evaluate high-throughput (HT) tools and models. The toxicology community is working to increase the speed of toxicity testing by developing new technologies to transition from an inefficient, costly, and animal-centric process to one that seeks a better understanding of disruptions of important biological processes using HT screening bioassays.[3,4] Complementary efforts are underway to develop quantitative exposure estimates in a rapid, efficient manner through models requiring only minimal information.[5-8] These models differ in scope with respect to exposure sources, with some focused on the fate and transport of a chemical following release into the environment (far-field), and others focused on understanding exposures resulting from use of consumer products, mostly indoors (near-field). This categorization of sources and models into near-field and far-field,[5,9] and the additional categorization of near-field sources into direct (releases immediately on or proximate to the body) and indirect (releases within the residential microenvironment)[10] have recently proven useful in chemical exposure estimation.

Consumer products contain and release an array of potentially hazardous chemicals to which individuals may be exposed via direct or indirect sources.[11-15] A growing number of chemicals are constantly being incorporated into an expanding portfolio of household products;[16] accordingly, the most important pathways of exposure to a great many chemicals may be associated with

63 consumer product use.[5] Results from USEPA's Total Exposure Assessment Methodology
64 (TEAM) field studies of the early 1980s suggested that not only did indoor sources of toxic
65 chemicals greatly outnumber outdoor sources, but that the proximity of the sources and the limited
66 opportunity for dilution produced greater exposure intensity.[17,18] More recently, a modeling effort
67 for exposure-based screening of chemicals that combined far-field focused exposure models with
68 a reverse pharmacokinetics evaluation of biomarker data provided further evidence that chemicals
69 associated with consumer product use are most often associated with the highest exposures.[9]
70 Until the European Union promulgated the Registration, Evaluation, Authorisation and
71 Restriction of Chemical (REACH) regulation, exposure assessments in residential settings had
72 largely focused on one or only a few chemicals at a time, as HT exposure predictions for consumer
73 products require estimates of multi-chemical signatures of exposure, uptake and body burden,[19-22]
74 which in turn require information on the chemical composition of consumer products. New
75 databases containing such information[23,24] have made HT approaches more attainable.
76 Over the past decade, USEPA has developed a series of predictive exposure models for
77 chemicals using the Stochastic Human Exposure and Dose Simulation (SHEDS) framework. Most
78 of the SHEDS models are high-tier, longitudinal models which use many inputs to characterize in
79 detail the variability and uncertainty in population exposures using demographic, exposure factor,
80 and chemical application data, in combination with human activity and location
81 (microenvironment) information from EPA's Consolidated Human Activity Database
82 (CHAD).[25,26] The SHEDS models, which can examine both residential and dietary sources of
83 exposure, have been successfully developed and applied for organophosphate and pyrethroid
84 pesticides,[27-31] arsenic,[32-34] and methyl mercury.[35] Such probabilistic models are extremely useful
85 for assessing the risks from a single chemical of concern, but can be slow and burdensome to run,

86 often requiring a large number of chemical-specific inputs. Based on the SHEDS Model for
87 Multimedia, Multipathway Chemicals (SHEDS-MM),[36] a leaner, more versatile model has been
88 developed: SHEDS-High Throughput or SHEDS-HT. SHEDS-HT is the first SHEDS model
89 designed to be run as a lower-tier model, with relatively few inputs and a fast execution speed.
90 This allows SHEDS-HT to be applied quickly to a large number of chemicals. The model has the
91 potential to generate population distributions of daily-level exposures and intake doses (mg/kg-
92 body weight/day) for a range of chemicals present in residential environments, foods, and drinking
93 water in a HT capacity.

94 Here, we describe the development of SHEDS-HT and its initial application to over 2500
95 consumer product ingredients and agricultural pesticides. Through this case study we demonstrate
96 the potential of the model for understanding and evaluating key factors contributing to chemical
97 exposures and for characterizing the impact of variability and/or uncertainty in the input
98 parameters on exposure and dose predictions. We also demonstrate the ability of the model to
99 reproduce high-tier results for an individual chemical, and present a comparison of the case study
100 model results against available exposure predictions developed from biomarker measurements
101 from the National Health and Nutrition Examination Survey (NHANES).

102 ## METHODS

103 ### Development of SHEDS-HT from SHEDS-Multimedia

104 The original SHEDS-MM model is capable of producing detailed year-long pathway-specific
105 chemical exposures for a population of simulated individuals based on temporally-resolved human
106 activity data. SHEDS-HT, in contrast, is a cross-sectional model that produces daily-level
107 pathway-specific exposures and intake doses (mg/kg/day), removing within-day temporal detail
108 and associated data requirements. Throughout the development of SHEDS-HT, iterative variance

decomposition-based sensitivity analyses[37] and other tests were performed in order to decide which model inputs, parameters, and algorithms were required to be retained in the model to accurately reproduce distributions of average daily exposures.

There are several other key differences between SHEDS-MM and SHEDS-HT. SHEDS-MM is coded in SAS (v. 9.3; Cary, NC), a proprietary environment; SHEDS-HT is coded in the R language (v. 2.15.3), which is freely available.[38] A reduced version of an indoor fugacity model[39] has been incorporated into SHEDS-HT as a source-to-concentration module for predicting indoor environmental concentrations. In addition, direct near-field exposure scenarios (such as direct dermal, inhalation, and incidental ingestion) have been added. In SHEDS-HT, dietary ingestion via food and drinking water ingestion pathways has been seamlessly combined with the near-field exposure predictions to product aggregate exposures.

Chemical, Pathway, Scenario, and Route Domains of SHEDS-HT

The chemical domain of SHEDS-HT is currently organic chemicals, as the properties of these chemicals can be parameterized (with admitted uncertainty) in a HT manner using quantitative structure-activity relationship (QSAR)-based tools such U.S. EPA's Estimation Program Interface (EPI) Suite.[40] Due to lack of information, SHEDS-HT does not explicitly include dissociation for ionogenic compounds in its indoor fate and transport or chemical absorption (e.g. dermal) algorithms, although some impacts could be incorporated via use of the model's chemical-specific inputs (e.g., properties) if data were available.

The exposure scenarios in SHEDS-HT are summarized in Table 1, with their corresponding exposure routes and data streams. The near-field direct scenarios reflect exposure during the use of a consumer product, whereas indirect exposures result from incidental contact with air and surfaces after the original usage event. The direct dermal scenarios involve the application of

products to one's skin (e.g., soap, sunblock); incidental direct dermal exposures can also occur during the use of other products (e.g., cleaning products, insecticides). The direct ingestion scenario involves the non-intentional (non-dietary) ingestion associated with direct product use (e.g., toothpaste, lipstick). Certain consumer products (e.g., those in spray formulations or those containing chemicals with high vapor pressures) result in exposures via inhalation of vapor or aerosol mass. The hand-to-mouth exposure route accounts for chemical transferred to the mouth from the hands and fingers, and is modeled for both direct and indirect chemical sources. The object-to-mouth route, which is modeled for the indirect pathway, is intended to capture the behavior of young children who pick up objects (e.g., toys) and chew or suck on them.

SHEDS-HT Modules and Methods

The general SHEDS-HT methodology involves merging multiple data streams to parameterize the probabilistic exposure model in the manner as shown in Figure 1 and Figure S1 of the Supporting Information (SI). The near-field pathways, scenarios, and routes that are active for a given chemical in SHEDS-HT are determined by the consumer product category (or categories) that are associated with that chemical in the input database; each chemical-category pair has assigned chemical composition information (mass fraction distributions and a prevalence factor describing the fraction of category formulations containing the chemical). Each category, in turn, has assigned usage patterns. Chemicals can also be found in various food groups or in drinking water. These input data streams are provided to SHEDS-HT via a text file that fully parameterizes each active exposure scenario for each chemical. This flexible approach allows for any set of consumer product categories or food group definitions to be used, as long as they are linked with available SHEDS-HT scenarios, and parameterized with the required information.

A full description of the exposure equations used in SHEDS-HT and their corresponding input parameter distributions are given in Section A of the SI; each SHEDS-HT module is described briefly below.

Population Module

U.S. Census-based input data are used to generate a simulated population representative of the U.S. population in terms of age and gender; a population of many thousands of individuals can be handled by the model. All active exposure pathways for a chemical are modeled for this simulated population, and aggregate exposures for each person (with contributions from all active pathways, scenarios, and routes) are calculated. After the population is created, Monte Carlo methods are used to assign relevant exposure factors and cohort-matched activity and food intake diaries to each person.

The default SHEDS-HT activity diaries are daily-level diaries obtained by summarizing the event-level human activity diaries provided in CHAD.[25,26] The default SHEDS-HT food diaries are based on the National Health and Nutrition Examination Survey-What We Eat in America (NHANES-WWEIA) 1999-2006 two-day food intake diaries,[41] processed to calculate the mass of each food group consumed by the individual. SHEDS-HT by default considers a set of 41 crop groups (Table S7) defined by EPA and used for establishing pesticide tolerances,[42] although other food groups can be used.

Indoor Fugacity Module

The source-to-concentration module used in modeling the indirect near-field exposures is based on the indoor fugacity model initially presented for pesticides in Bennett and Furtaw[39] and subsequently applied to other chemicals with indoor sources.[43,44] An implementation of this model was analyzed using variance decomposition-based sensitivity analyses developed for SHEDS[37] to

identify the model inputs influencing average daily air and surface chemical concentrations given a fixed chemical mass application. The analysis demonstrated that the concentrations in treated and untreated compartments were most influenced by the same limited set of model parameters, specifically air exchange rate with the outdoors, degradation rate on surfaces (D_s), boundary layer and floor effective thicknesses, solubility (S), octanol-water partition coefficient (K_{ow}), and vapor pressure (VP). In every compartment, these variables alone accounted for greater than 95% of the variance in concentration, with VP being the largest contributor in all compartments. Only D_s, K_{ow}, S, and VP are chemical-specific. The strategy for implementation into SHEDS-HT was to reduce the model in such a way retain these parameters as chemical-specific model inputs, while hardcoding other parameters with default values or distributions. The molecular weight (MW) and the decay rate in air (D_a) had little contribution to the variance (<1% for MW and <3% for D_a) but were also retained as model inputs since they could be estimated for a wide variety of chemicals by EPI Suite.[40] In addition, the final number of compartments in the model was reduced to two (air and surfaces), since SHEDS-HT doesn't discriminate between treated and untreated areas in the home (in terms of contact). Sensitivity analysis results, input distributions, and final equations for the fugacity module are given in Section B of the SI.

Indirect Exposure Module

Exposures via the indirect pathway result from individuals breathing indoor air or touching contaminated surfaces. The fugacity module is used to model media concentrations in the residence as functions of time, based on the mass and frequency of use of consumer products. Concentrations on surfaces include chemical found in both the bulk phase and in dust. The individual is exposed to these concentrations via inhalation, dermal, and object-to-mouth routes via contact with the contaminated media as described in Section A of the SI. The amount of contact

time with each chemical-containing medium in the residential microenvironment is determined from the activity diary for the individual and user-defined contact probabilities (Table S3). The resulting dermal exposures are subsequently available for non-dietary ingestion via hand-to-mouth dermal removal (described below).

Direct Exposure Module

Direct exposures (inhalation, dermal, and ingestion) are parameterized similarly to other available equations for these routes, such as those available in ConsExpo[45] and the Exposure and Fate Assessment Screening Tool (EFAST) consumer exposure module.[46] Probabilistically-predicted exposures for all routes are dependent on category-specific use frequencies, population prevalences, masses, and compositions. Dermal exposures also consider the fraction of product in contact with the skin and fraction retained on the skin post-use (which differ for products that are washed off versus left on), whereas ingestion exposures (e.g., for lip products) are based on a fraction of mass that is ingested during use. As with the indirect pathway, the dermal exposures are subsequently available for ingestion via the hand-to-mouth route. Direct inhalation exposure can occur via intake of vapor or aerosol mass during use.

Dietary Exposure Module

Dietary exposures are calculated by determining the total daily mass of chemical intake for each simulated person via different foods and/or drinking water. Concentration distributions for each relevant food group are provided as input. For each simulated individual, daily chemical concentrations (μg of chemical per g of food) are sampled (one for each food group). Dietary exposures are calculated as the sum (over food groups) of the product of concentration and mass of food consumed (as determined by the assigned food diary for the person).

Exposure Aggregation, Dermal Removal Processes, and Intake Dose

After exposures from all scenarios are calculated for a chemical, SHEDS-HT aggregates exposures across scenarios and pathways, applies dermal removal processes, and determines the final intake dose (mg/kg/day) for the simulated person. The dermal exposures obtained via both direct and indirect pathways are summed and made available for removal by five related processes: bathing, hand-washing, rub-off, hand-to-mouth transfer, and dermal absorption. Chemical transfered to the mouth results in non-dietary ingestion exposure.

Intake dose estimates are calculated using distributions of route-specific fractional absorptions. Dermal absorption fraction distributions are chemical-specific, as they are linearly scaled via predicted dermal permeability coefficients (K_p) across chemicals (eq. a27 in the SI). Currently, distributions for absorption fractions for the inhalation and ingestion pathways are the same for all chemicals (Table S2).

Initial Case Study: Chemicals in Consumer Products and Pesticides in Foods and Drinking Water

SHEDS-HT was applied to a case study of 2507 chemicals in consumer products and pesticides for a simulated population of 10,000 individuals. The parameterization of the model for this case study is described below; final counts of chemicals, consumer products, and categories associated with each scenario are given in Table S6.

Consumer Product Chemical Composition Data

The composition data used in the case study were obtained from two existing databases of chemical ingredients in consumer products. The first database was USEPA's Consumer Product Chemical Profile Database (CPCPdb),[24] which contains information on 1797 chemicals found in

8921 consumer products derived from retailer-provided Material Safety Data Sheets (MSDS). The second database was the National Library of Medicine's Household Products Database (HPDB),[23] which is also based on collated MSDS data and includes 3864 chemicals and proprietary substances in 12073 products. This case study focused on "consumable" products (i.e. those used in the home and replenished periodically), so products such as pharmaceuticals and articles were excluded from both databases. In total, usable data were extracted for 2177 consumer product chemicals.

All products in both databases were mapped to a harmonized set of 254 categories for assignment of usage patterns and active exposure scenarios. If a chemical was found in any product within a consumer product category, it was assumed to be in all products in the category (a 100% chemical prevalence rate). This assumption represents the worst-case situation for each individual consumer product category (i.e. a user is always assumed to use a formulation containing the chemical). This is the most conservative assumption given the lack of knowledge about the 1) market share of individual products in the databases and 2) the prevalence of the chemical in formulations not represented in the databases. Chemicals in the databases having no reported composition data were assigned distributions of compositions derived from all reported data for the corresponding category.

Assignment of Product Use Information and Scenarios to Harmonized Categories

The consumer product use patterns developed for the case study included percent of the population using the product (prevalence), frequency of use, and amount of product (g) per use, and were age- and gender-dependent where appropriate. The input parameters were developed from a review of the available literature on consumer product use,[47-67] including both survey measurements and default assumptions from other exposure models. Consensus values were

selected if multiple sources existed for a parameter; where data were not available, default values were assumed using judgment. The usage parameter values for each category and the corresponding data sources are given in Table S8 of the SI. Corresponding active exposure scenarios were also mapped to each category (Table S9).

Chemical Residues in Foods

For the case study, distributions of residues in foods and drinking water were obtained for 330 pesticides from the U.S. Department of Agriculture's Pesticide Data Program (PDP) databases.[68] These databases contain measurements of pesticide concentrations in a variety of agricultural commodities collected from 1997-2011. These data were processed to assign commodities to the food groups used by SHEDS-HT. In this initial analysis, the fraction of the residues that were non-detects were assigned zero concentrations, while the detected residues were fit to food group-specific lognormal distributions using maximum likelihood estimation.

Chemical Properties

Chemical properties required by SHEDS-HT (given in Table S4) were estimated for all chemicals in the case study using EPI Suite.[40] Degradation rates on indoor surfaces are difficult to quantify (as little data are available), yet they are anticipated to be slower than reported degradation rates on outdoor surfaces, particularly for semivolatile organic compounds.[14] As an initial assumption, degradation rate was assumed to be equal to the mean of the rates associated with the (relatively slow) soil and sediment half-lives predicted by EPI Suite, with the acknowledgment that this may contribute significantly to uncertainty and is therefore a critical parameter to be considered in the sensitivity analysis discussed below.

Variability and Uncertainty in Model Inputs and Sensitivity Analyses

Variability in exposure results from true heterogeneity across locations, people, or time. The 1-D Monte-Carlo application performed here represents the combined variability and uncertainty associated with each of the inputs. SHEDS-HT is a probabilistic model that requires analytical distributions, empirical distributions, or survey data to develop inputs. The choices of input form were made depending on available sample size and specifics of the datasets available. The probability distributions or databases used for each model input parameter (and their data sources) are given in Tables S1, S2, and S5. For chemical properties, distributions were assumed to be lognormal with a geometric mean equal to the estimated value. A nominal value of GSD=1.5 was selected for the case study based on results from analysis of similar data (e.g., vapor pressures) obtained for previous higher-tier SHEDS applications; however, these are chemical-specific inputs to the model and other distributions could be used. Mean and variability (i.e., coefficient of variation) of consumer product chemical compositions were derived from the CPCPdb and HPDB datasets; these distributions were also assumed to be lognormal. The variables quantifying consumer product use patterns were assumed to be more uncertain. These parameters were given lognormal distributions with mean values as described above and a coefficient of variation of 100%.

A sensitivity analysis was conducted to determine the impact of key model inputs on resulting total intake doses (mg/kg/day). This analysis explored one model input variable at a time using a percentile-scaling method previously employed for other SHEDS analyses.[33] Briefly, a set of candidate model parameters were selected for analysis, and base case SHEDS-HT runs were performed with these parameters fixed at their median values, while all other parameters were allowed to vary probabilistically. Two more additional runs were performed for each candidate

311 input, using lower and higher values than the base case and chosen to represent the range covered
312 by the variability distribution for each input, namely the 5th percentile and the 95th percentile for
313 each. Finally, ratios of the high-to-median and low-to-median model results were calculated,
314 allowing ranking of the parameter influence associated with the full range of estimated variability
315 and uncertainty.

316 **Evaluation of SHEDS-HT**

317 A model-to-model comparison with SHEDS-MM was performed to confirm that the exposure
318 distributions generated by SHEDS-HT for average daily exposures reproduced those predicted by
319 the higher-tier model. These comparisons were done for a case study of permethrin exposure
320 following a crack-and-crevice application in the home, using previously-developed inputs.[31]
321 SHEDS-HT exposures were compared with the fourth day post-application of the chemical
322 treatment in SHEDS-MM. This comparison included only the indirect pathways, as direct
323 exposure scenarios are not considered in SHEDS-MM.

324 SHEDS-HT results were also compared with available biomonitoring-based exposure data.
325 Predictions were compared to oral equivalent intake doses recently estimated from biomarker data
326 from NHANES using reverse pharmacokinetic modeling.[9]

327 **RESULTS**

328 **SHEDS-HT Performance**

329 Runs for the 2507-chemical case study (for a population of 10,000 individuals), performed on a
330 Windows-based system desktop with an Intel Xeon 2.66 GHz processor and 4.0 GB RAM,
331 required approximately 8 hours (10-20 seconds/chemical). However, the time per chemical was
332 influenced by the number of active exposure scenarios. In contrast, a SHEDS-MM variability run

of only 1000 individuals for a single chemical on a similar machine requires about one hour (for the residential module alone).[69] Thus, SHEDS-HT can perform large runs (e.g. large numbers of chemicals, large populations, or sensitivity and uncertainty analyses) that would take prohibitively long using SHEDS-MM.

Comparison of SHEDS-HT with SHEDS-Multimedia

SHEDS-HT was able to reproduce distributions of SHEDS-MM average daily exposures and mean intake dose (Figure S2). The very high end (99^{th} percentile) of dose (mg/kg/day) was about 20% larger in SHEDS-HT, probably because a single sampled high-percentile value from a distribution (e.g. an exposure factor) can apply for the entire day in SHEDS-HT. The contributions to the mean daily intake dose from the various pathways for SHEDS-HT vs. SHEDS-MM were also comparable: 91.3% versus 90.0% for hand-to-mouth ingestion, 0.2% versus 0.2% for inhalation, 6.8% versus 6.7% for dermal, and 2.9% versus 3.0% for object-to-mouth ingestion. However, we note that we plan in the future to make similar comparisons for additional chemicals, as different chemical properties and chemical sources will likely result in different exposure patterns.

Exposure Predictions for Case Study Chemicals

Final intake dose predictions (mg/kg/day) for the 2507 chemicals are shown in Figure 2. The predicted nonzero intake doses spanned 13 orders of magnitude, due to significant impact of high variability and uncertainty in the model inputs but indicating also that a good discrimination among chemicals for the purpose of prioritization remains feasible.

The distributions of intake dose were highly skewed, with the mean dose falling between the 75^{th} and the 95^{th} percentile. The mean doses ranged from 0 to 6.88 mg/kg/day, with means for 85% of the chemicals falling between 1.0E-7 and 0.1 mg/kg/day. The highest population median intake

dose for any chemical was 0.18 mg/kg/day (for glycerol, which was present in 90 different consumer product categories); the 25 chemicals having the highest predicted median doses are given in Table S10. Note that for some chemicals, the mean exceeded even the 99th percentile. This was due to being an ingredient of products with very low population prevalences and/or frequencies, but with large potential exposures, resulting in relatively high values for a few individuals driving the population mean. An example is isobutyl alcohol, which was only found in finishes and paints. While 40% of adults use interior or exterior paint, the mean of the use frequency was only 2/year, so in this cross-sectional analysis only 0.2% of people will use it on a given day, resulting in zero exposure for the 99th percentile. This highlights that care needs to be taken in interpreting percentiles for chemicals in infrequently-used products, and that separate analyses for subpopulations with specific product-use habits will be important.

Distributions of predicted intake doses for different cohorts are ranked in Figure 2 (bottom) by mean exposures for children age 0-5. In general, greater intake doses were seen in females than in males, due to lower mean body weights and higher prevalence of use of personal care products by women. Children age 0-5 typically had the highest intakes, due to having lowest body weights, highest hand-to-mouth activities, and highest percentages of time spent in the residence. The chemicals at the right of the panel are those to which no children were exposed in the 10,000 person simulation, due to zero prevalence of use of corresponding products for children.

Intake dose predictions by pathway-scenario are given in Figure S3 of the SI. In general, chemicals having the highest mean intake doses exhibited high intakes from direct dermal, direct ingestion, and indirect scenarios. Intakes from these scenarios were major contributors across a wide range of chemicals. This predicts importance of indirect near-field sources, which are neglected in many screening-level models.

Dietary intakes were significant contributors (for chemicals having the pathway), while direct inhalation intakes (aerosol and vapor) were typically several orders of magnitude lower. Route-specific contributions to intakes associated with direct dermal and indirect scenarios are given in Figure S4. For most chemicals with these scenarios, non-dietary ingestion (e.g., via the hand-to-mouth route) was a larger contributor to intake dose than dermal absorption or inhalation (in the case of indirect scenarios).

Mean predicted exposures by category are given in Figures S5 (aggregated consumer product categories) and S6 (subset of specific categories having the highest exposures). The boxplots examine the distribution of population means across chemicals for both children 0-10 and adults. Pesticides exhibited the highest mean exposures for children, while personal care products produced the highest exposures for adults (due to higher prevalence of use and reduced hand-to-mouth activities when compared to children). The highest individual categories for adults were products with high probabilities of non-intentional ingestion in combination with high frequency of use (e.g. toothpaste, lip products, denture creams) whereas for children, dermal products with high frequencies of use (e.g. sunscreen, diaper creams) were highest, due to increased hand-to-mouth behaviors.

Sensitivity Analysis

The results of the initial sensitivity analysis for total intake dose are provided in Figure S7. The boxplots characterize the distribution of the sensitivity indices across chemicals; all sensitivity indices were less than one order or magnitude. The index for mass applied is a point, since the model is linear in mass when this variable is varied uniformly across consumer product categories (as here). Given the estimated variability/uncertainty in the model parameters, the intake dose is most influenced by consumer product use variables (i.e. mass applied and frequency of use),

consumer product composition, and variables describing the magnitude of the hand-to-mouth exposure pathway (e.g. hand-to-mouth frequency, dermal transfer coefficient, and hand washing frequency). This indicates a need to better characterize these variables. The chemical degradation rate on indoor surfaces had a small impact compared to other variables, but this parameter is still highly uncertain (i.e. the use of estimated soil and sediment half-lives may be inadequate), and better characterization of degradation rates indoors is a need for future research.

Comparison of SHEDS-HT Results against Predicted Exposures from NHANES

Median predicted intake doses are plotted against values for 39 chemicals estimated from NHANES biomarker data[9] in Figure 3. The median SHEDS-HT intake doses were significantly correlated with the predicted NHANES median oral equivalent doses ($p<0.0001$, $R^2=0.39$; $R^2=0.47$ when the observed outlier for chlorpyrifos-methyl is ignored). Overall, the SHEDS-HT distributions (bottom panel) were higher than the NHANES values; this overestimation of exposure is not unexpected, as current factors that contribute to this overestimation may include 1) assumption of 100% prevalence of chemicals in formulations within consumer product categories, 2) assumption that mass used in indirect scenarios is retained on indoor surfaces post-application (not wiped up), and 3) selection of conservative default values for some critical use pattern variables (e.g., frequency of use, percent of product ingested). In addition, the NHANES-based exposure numbers are also model estimates and thus subject to variability and uncertainty.

DISCUSSION

Exposure-Based Chemical Prioritization

The SHEDS-HT framework described herein provides an efficient platform for HT, screening-level simulations of exposure to chemicals via multiple scenarios and routes for use in chemical prioritization. The unique advantage of this exposure model is its ability to identify and quantify

the major sources, pathways and assumptions that influence prediction of chemical-specific exposures or dose. Moreover, SHEDS-HT relies upon real-world human use, physical transport/transformation, and contact processes that frequently have stochastic and chemical-specific characteristics. The model structure facilitates sub-modular and full model evaluation, thereby facilitating flexible and quick updates to input data steams used, model parameters chosen, and refinements to exposure algorithms currently employed. Its modular design also allows for expansion beyond the current exposure scenarios without any major code restructuring. We anticipate the model will be made available to the public following the conclusion of USEPA administrative review.

Model Limitations and Uncertainties

The intake dose predictions presented here should be interpreted in a manner consistent with the high uncertainties associated with the various model input data (e.g., limitations of using QSAR-based chemical properties, such as those noted by Arnot et al.[7]) Simplifying algorithmic choices (e.g., the use of dermal absorption fractions rather than loading-dependent models that incorporate flux,[70] ignoring dissociation) contribute additional uncertainty. A key area of future research will be the incorporation of improved route-specific absorption algorithms. In the future we also plan to investigate the effect of separating variability from uncertainty and to apply a bootstrap-based uncertainty analysis technique.[33] We are also refining the key model inputs and algorithms to the extent possible to reduce the uncertainty built into our modeling assumptions related to consumer products by developing appropriate information both chemical prevalence within consumer product categories and market share information for product formulations. Another area of future research should be the continued evaluation of the indoor fugacity model against available media measurements and further assessment of the impact of the simplifying assumptions of the reduced model (e.g., combination of carpet and vinyl compartments) on resulting indirect exposures.

However, even considering these limitations, a significant portion of the variance in the predicted NHANES medians was explained by the SHEDS-HT results. Chemicals for which the NHANES predictions were higher (diethyl pthalate, chlorpyrifos methyl) were likely indicative of missed sources (e.g. exposure from articles) or related to biases created by the assumption of 0 concentrations for non-detects in foods from the PDP database. Adding additional exposure sources and pathways to SHEDS and refined handling of non-detects in input databases should allow for improved quantification of these biases.

Further Evaluation

We are now performing a more detailed comparison of the SHEDS-HT exposures (and other near-field exposure predictions) to the biomonitoring-based exposure data within a systematic empirical evaluation framework,[9,71] which will allow 1) iterative evaluation of the predictive power of the model across different chemical classes, 2) quantification of the value added by model refinements (e.g. addition of new chemical sources and scenarios or improved chemical-specific intake algorithms), and 3) estimation of uncertainties. This evaluation is critical in understanding and quantifying the utility of any SHEDS-HT predictions in light of the numerous limitations of this HT model. Ultimately, the evaluation framework also allows for the combination of SHEDS-HT results with results from other near-field and far-field exposure models to produce consensus predictions for large numbers of chemicals, and provides a means by which to evaluate the suitability of such models for rapid risk-based prioritization.

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Supporting Information Available

Additional information as noted in text. This information is available free of charge via the Internet at http://pubs.acs.org/.

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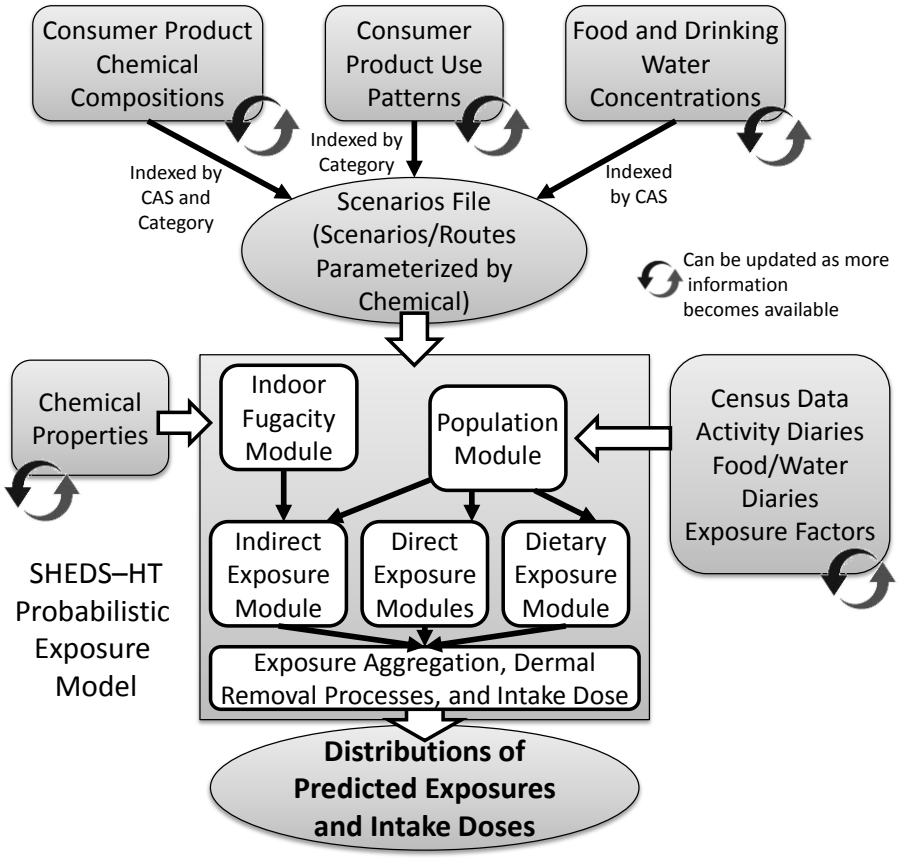

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700 Figure 1. SHEDS-HT input data streams and modules.
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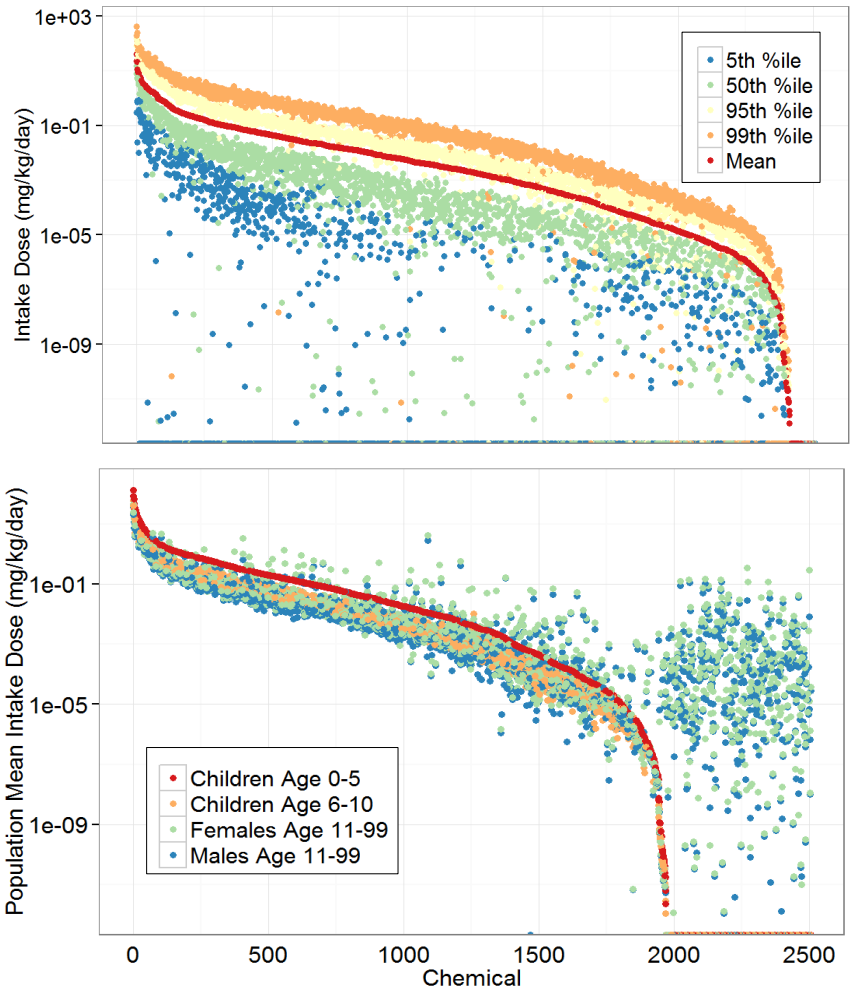

Figure 2. SHEDS-HT results for 2507 organic chemicals with near-field sources. Top: Percentiles of total intake dose for all ages. Bottom: Mean total intake dose by age/gender cohort, sorted by the mean values for children ages 0-5 years.

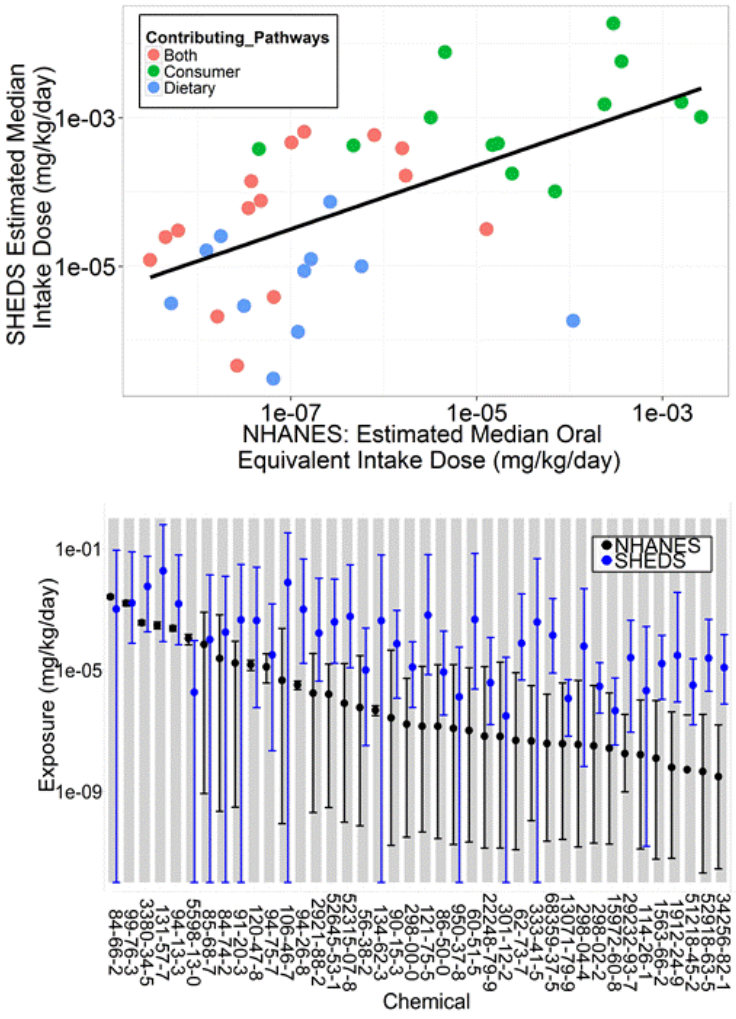

Figure 3. SHEDS-HT predicted chemical intake doses compared to oral equivalent intake doses inferred from NHANES biomarker data for 39 chemicals. Top: SHEDS median intake dose versus biomonitoring-based predicted median intakes. Bottom: SHEDS median predictions (whiskers indicate population 5th and 90th percentiles) compared to median predictions inferred using NHANES[9] (whiskers indicate uncertainty in median prediction).

717 Table 1. SHEDS-HT exposure pathways, scenarios, and routes with required input data. Not all
718 scenarios must be modeled for all chemicals.

Pathway	Scenarios	Routes	Required Data Streams
Near-field direct	Dermal exposure (either via direct application of personal care products to the body or incidentally during household use of other products) Inhalation of vapor during use of consumer products Inhalation of aerosol mass during use of consumer products	Dermal Inhalation Ingestion (direct ingestion plus incidental non-dietary ingestion via hand-to-mouth transfer of chemical in product applied directly to skin)	Consumer product chemical composition Consumer product use patterns Chemical properties Time-activity data (determine ventilation rates) Various exposure factor distributions (including hand-to-mouth behavior and other microactivities)
Near-field indirect	Application of consumer products to household surfaces, air, or pets Emission of chemicals from consumer articles or building products	Dermal Inhalation Ingestion (incidental non-dietary ingestion via object to mouth and hand-to-mouth transfer of chemical found on indoor objects and surfaces, including in dust)	Consumer product chemical composition Chemical emission rates from articles or building materials Consumer product use patterns Consumer product article or building material use patterns Chemical properties Fate-related properties of the indoor environment (e.g. air exchange rates, dust loadings) Time-activity data (determine time spent in residence and ventilation rates) Various exposure factor distributions (including hand-to-mouth behavior and other microactivities)
Dietary	Consumption of contaminated food or drinking water (from agricultural chemical use or leaching from food packaging)	Dietary ingestion	Chemical concentrations in foods and drinking water Population food and water intakes

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