Quantifying Children's Aggregate (Dietary and Residential) Exposure and Dose to Permethrin:
application and evaluation of EPA's probabilistic SHEDS-Multimedia model

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ABSTRACT

Reliable, evaluated human exposure and dose models are important for understanding health risks from chemicals. A case study focusing on permethrin was conducted because of this insecticide's widespread use and potential health effects. SHEDS-Multimedia was applied to estimate U.S. population permethrin exposures for 3-5 year-old children from residential, dietary, and combined exposure routes, using available dietary consumption data, food residue data, residential concentrations, and exposure factors. Sensitivity and uncertainty analyses were conducted to identify key factors, pathways, and research needs. Model evaluation was conducted using duplicate diet data and biomonitoring data from multiple field studies, and comparison to other models. Key exposure variables were consumption of spinach, lettuce, and cabbage; surface-to-skin transfer efficiency; hand mouthing frequency; fraction of hand mouthed; saliva removal efficiency; fraction of house treated; and usage frequency. For children in households using residential permethrin, the non-dietary exposure route was most important; when including all households, dietary exposure dominated. SHEDS-Multimedia model estimates compared well to real-world measurements data; this exposure assessment tool can enhance human health risk assessments and inform children's health research. The case study provides insights into children's aggregate exposures to permethrin and lays the foundation for a future cumulative pyrethroid pesticides risk assessment.

Key Words: probabilistic, exposure, model, aggregate, SHEDS, permethrin

INTRODUCTION

Reliable, evaluated exposure models are important for improving human health risk assessments. They can answer questions such as: What is the population distribution of exposure, dose, and risk for particular groups and lifestages? What are the time patterns of exposure? What are key media, pathways, and factors to inform how to effectively reduce exposures and address the greatest uncertainties for assessing risk? Implementation of the Food Quality Protection Act of 1996 (FQPA) necessitated developing new methodologies to assess residential exposures as well as refined dietary estimates. While historically used "lower tier" modeling approaches may be appropriate for obtaining conservatively high screening level estimates of exposure, dose, and risk, higher tier models are needed for more realistic estimates for which uncertainties can be quantified. Probabilistic models have been recommended by the National Academy of Sciences (NAS, 2007) and the EPA's Council for Regulatory Environmental Models (U.S. EPA, 2008a). The Stochastic Human Exposure and Dose Simulation model for multimedia, multipathway chemicals (SHEDS-Multimedia) is a model developed by EPA's Office of Research and Development to help address these needs.

SHEDS-Multimedia is a physically-based probabilistic computer model that can simulate aggregate or cumulative human exposure and dose, via dietary and residential routes, to a variety of environmental chemicals (http://www.epa.gov/heasd/products/sheds_multimedia/sheds_mm.html). This model can be used to predict ranges of exposure in a population; to identify critical pathways, factors, and uncertainties; and to enhance dose model estimates (Glen et al., 2010; Zartarian et al., 2008). The purpose of SHEDS-Multimedia is to improve the understanding of aggregate and cumulative exposures over space and time for enhanced human health risk assessments involving chemicals such as pesticides, metals, and persistent bioaccumulative toxicants. Because it uses 2-stage Monte Carlo sampling, SHEDS-Multimedia can quantify variability in population exposure and dose estimates, and the uncertainty associated with different percentiles. Another key feature of the model is the use of a time series approach for simulating dietary and residential exposures, accounting for variability within a day from separate eating occasions and microactivities. The sequential diary-based approach overcomes limitations of summing daily exposures from individual pathways. Tracking sequential dermal hand and body exposures, and linking hand-to-mouth ingestion time series with dermal hand exposures, accounts for both replenishment and removal processes (i.e., surface contact, hand mouthing, hand washing, bathing, absorption into the skin). The newest version of SHEDS-Multimedia (version 4) also includes several longitudinal diary assembly methods, multiple chemical (as well as single chemical) algorithms for conducting cumulative and aggregate assessments, and a number of other unique or advanced features. For example, the model permits correlation of randomly sampled inputs; simulates co-occurrence of chemical usage and application scenarios; includes multiple methods for sensitivity and uncertainty analyses; and is transparent and flexible for simulating different exposure scenarios. SHEDS-Multimedia exposure profiles can be linked to physiologically-based pharmacokinetic (PBPK) models for enhanced dose and risk quantification.

Current and earlier versions of SHEDS-Multimedia have been used in EPA, academia, government, and industry for a variety of regulatory and research purposes (e.g., Tulve et al., 2011; Xue et al., 2010a; Xue et al., in review; Stout et al., 2009a; Georgopolous et al., 2008;

California EPA, 2007; Zartarian et al., 2006; Xue et al., 2006; Hore et al., 2006; Stout and Mason, 2003; Buck et al., 2001; Zartarian et al., 2000). The most recent versions of SHEDS-Multimedia (versions 3 and 4, respectively) were externally peer-reviewed by the EPA's Office of Pesticide Programs (OPP) Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) (FIFRA SAP, 2007, 2010). Evaluation has been conducted on the separate dietary and residential modules, and the combined results, with model-to-model comparisons and comparisons of model estimates against available environmental and biomonitoring data (http://www.epa.gov/heasd/products/sheds_multimedia/files/SHEDS%20Model%20Evaluation.pdf).

This paper presents the application of SHEDS-Multimedia to an aggregate permethrin case study for 3-5 year-old children, including variability, sensitivity, and uncertainty analyses, along with model evaluation results. SHEDS is comprised of both a residential module (SHEDS-Residential version 4.0; Glen et al., 2010; Isaacs et al., 2010a), and a dietary module (SHEDS-Dietary version 1.0; Xue et al., 2010a,b; Isaacs et al., 2010b) linked by a methodology presented below. Permethrin, a synthetic pyrethroid insecticide, was selected for this model application because of (1) potential health effects (USEPA, 2006, 2007; Kim et al., 2005; Rusiecki et al., 2009; Ecobichon, 1995), and (2) its widespread use, according to national measurement surveys, exposure field studies, National Health and Nutrition Examination Survey (NHANES) biomonitoring data, and use/usage data (Jacobs et al., 2003; CDC, 2009; Morgan et al., 2005, 2007; Naeher et al., 2010; Stout et al.b, 2009; Tulve et al., 2006, 2008; Wilson et al., 2004). It is the most commonly used pyrethroid pesticide, and the first pyrethroid being reviewed under FQPA.

METHODS

The SHEDS technical manuals describe in detail the model algorithms, methodologies, and input and output capabilities (Xue et al., 2010b; Glen et al., 2010). This case study quantifies population aggregate exposures for 3-5 year-olds (one of the EPA-recommended age groups (U.S. EPA, 2005) from both dietary ingestion and 9 residential application scenarios of permethrin.

Dietary Exposure Modeling

Model algorithms, key features, and earlier model evaluation efforts of the SHEDS-Dietary module are presented in Xue et al., 2010a, b. The United States Department of Agriculture (USDA) Continuing Survey of Food Intake by Individuals (CSFII) 1994-1996 and 1998 consumption data and the 1991-2006 USDA Pesticide Data Program (PDP) *cis*- and *trans*-permethrin residue database were used in the SHEDS-Dietary module to identify permethrin residue concentration ranges, age-related trends, and foods with higher permethrin residue concentrations. The Diversity and Autocorrelation (D & A) method (Glen et al. 2008) was used to construct longitudinal food consumption diaries. This method creates a population of longitudinal diaries that reproduce target values of the intra- and inter-person variance ratio (diversity, D) and day-to-day autocorrelation (A) for a key diary variable most relevant to exposure. Total caloric consumption was used as the key variable, with D and A statistics set to 0.3 and 0.1, respectively (based on longitudinal data from Lu et al. 2006; Alex Lu, personal communication).

Residential Exposure Modeling

The SHEDS Residential module is flexible and can be applied to a wide range of chemical exposure scenarios. For this permethrin case study, 9 residential exposure scenarios were selected based on analyses of usage information collected in the 2001-2002 Residential Exposure Joint Venture (REJV; Jacobs et al., 2003) consumer pesticide product use survey provided to the EPA: indoor crack and crevice (aerosol and liquid); indoor flying insect killer (aerosol); indoor fogger (broadcast); lawn (granular - push spreader and liquid – hand wand); pet treatment (liquid and spot-on); and vegetable garden (dust, powder). In addition, all 9 of these scenarios were combined in a single simulation. To address the specific exposure scenario(s) of interest, we used the input variables and data provided to the 2010 FIFRA SAP (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0015). These model input values are based on peer-reviewed publications, OPP's Residential Exposure Standard Operating Procedures (U.S. EPA, 1997a), recommendations by OPP's FIFRA SAP, EPA's Exposure Factors Handbook and Child-Specific Exposure Factors Handbook (U.S. EPA, 1997b, 2008b), and best Agency-derived estimates (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0015). To assemble one year longitudinal data, the D (diversity) & A (autocorrelation) method (Glen et al., 2008) was used with indoor awake time as the key variable (D=0.25, A=0.4) (Xue et al., 2004).

Linkage of Dietary and Residential Exposure Modeling

The methodology used to combine the dietary and residential module outputs (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0023; slides 34 and 35) was externally peer-reviewed (FIFRA SAP, 2010) and tested in this permethrin case study. We used the D & A method (Glen et al., 2008), with total caloric consumption as the key variable, to extrapolate the cross-sectional dietary exposure estimates into longitudinal food consumption patterns, and used waking time at home to extrapolate the residential cross-sectional activity patterns into longitudinal patterns. The dietary and residential longitudinal diaries were first binned separately by age and gender, and then matched by percentiles using additional binning variables: total caloric consumption weighted by body weight for dietary, and averaged MET (metabolic equivalent of task is an energy expenditure measure, i.e. the ratio of metabolic or energy consumption rate during a specific physical activity to the reference metabolic rate at rest) weighted by body weight for residential. An average of 50 to 100 data points in each bin was used as a criterion to select the key variables to ensure a large enough sample size in each bin for randomization.

Model Application with Permethrin Case Study

The SHEDS residential and dietary modules were each applied to estimate exposures for 3-5 year-olds, including both simulated use and non-use homes (i.e., where permethrin was or was not applied). The built-in pharmacokinetic (PK) model in SHEDS (Glen et al., 2010) along with available absorption rate data (fraction of administered dose) was used for the initial exposure pathway contribution analysis. A sample size of ~4000 individuals was used for the 1-year variability simulations. Results are reported for an annual averaging time and for separate and aggregated pathways. Sensitivity and uncertainty analyses were conducted to identify key factors, exposure pathways, and data gaps (Glen et al., 2010, chapters 5 and 6; Xue et al., 2010b, sections 2.6 and 2.7). Uncertainty analyses were conducted to assess whether there were sufficient data for consumption and residue data sources, and which dataset was relatively more important for exposure (assessing impact of residues versus consumption). We applied statistical bootstrapping of certain percentages of both datasets with the SHEDS-Dietary permethrin results (Xue et al., 2010b).

Two types of model evaluation were conducted for the permethrin analysis. First, SHEDS-Dietary modeled exposure predictions were compared against Children's Total Exposure to Persistent Pesticides and Other Persistent Organic Pollutants (CTEPP) Study duplicate diet data for *cis*- and *trans*-permethrin (data were matched by age and gender, based on 246 paired comparisons). Second, aggregate modeled SHEDS-PK dose predictions were compared to NHANES biomonitoring data for the urinary metabolites, *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*- and *trans*-DCCA) and 3-phenoxybenzoic acid (3-PBA) (DCCA and 3-PBA are non-specific metabolites for a number of pyrethroid pesticides). In addition, SHEDS was evaluated further against measurements in Tulve et al., 2011 and Xue et al., 2010a. The SHEDS Residential module compared well against other probabilistic aggregate residential exposure models in a model-to-model comparison using a simulated pyrethroid chemical (Young et al., in review). Dose estimates obtained using SHEDS linked with an aggregate permethrin PBPK model were compared against NHANES DCCA data (http://www.epa.gov/heasd/products/sheds_multimedia/files/SHEDS%20PBPK%20Permethrin%20Case%20Study.pdf).

RESULTS

Permethrin Population Exposure and Pathway Contribution Analyses

Table 1 shows summary statistics (in both mg/kg/day and µg/day) for the total (aggregated across dietary and residential pathways) annual averaged permethrin absorbed dose population estimates, based on 3825 simulated individuals: 2.4E-4 mg/kg/day (mean), 8.0E-4 mg/kg/day (95th percentile) and 2.0E-3 mg/kg/day (99th percentile). Analyses were conducted for the relative contribution to total absorbed dose by each of the SHEDS exposure routes. Table 1 and **Figure 1** present the contribution to annual average daily permethrin dose by exposure pathway for 3-5 year old children. The major exposure pathway for all 3-5 year old simulated children (i.e., including those residing in permethrin use and non-use households) in the U.S. population, based on means, was dietary ingestion (50%), followed by non-dietary ingestion (41%), inhalation (5%), and dermal (4%). For use households (i.e., 3-5 year old children living in homes treated with permethrin), Figure 1 shows that non-dietary ingestion was the key exposure pathway (61%), followed by dietary (26%), inhalation (8%), and dermal (5%).

Based on mean estimates, dietary and non-dietary ingestion routes are comparable (50% vs. 41%) considering all 3-5 year old children (i.e., those residing in permethrin use and non-use households). For permethrin use households, the non-dietary route is predominant (61% vs. 26%). At the 95th and 99th percentiles, the non-dietary ingestion route is the predominant route for all 3-5 year old children (use and non-use households) and for the use households only (http://www.epa.gov/heasd/products/sheds_multimedia/files/SHEDS%20Residential%20Module.pdf; slides 39 and 40).

Evaluation of SHEDS Modeled Permethrin Exposure and Dose Estimates

Table 2 shows that SHEDS-Dietary model results and CTEPP measurement results match well at the mean, 95th, and 99th percentiles for both *cis*- and *trans*-permethrin. Model estimates are much lower than measurements at lower percentiles. The ratio of mean modeled to measured results is 1.09 and 1.01 for the *cis*- and *trans*- congeners, respectively; the ratio of the 95th percentile modeled to measured results is 1.06 and 0.99.

Figure 2 compares SHEDS dose estimates, using the built-in PK model, against NHANES 3-PBA biomarker data. The ratios of modeled to measured estimates are 0.52, 0.23, 0.87, and 0.70 for the mean, 75th, 95th, and 99th percentiles, respectively. Model estimates are lower than measurements at less than approximately the 90th percentile.

Table 3 presents results of the SHEDS PK dose estimates against the NHANES *cis*- and *trans*-DCCA biomarker data. The ratios of modeled to measured estimates are 0.5-0.6 for the mean and upper percentiles.

Modeled Permethrin Exposure Sensitivity Analyses

The most important commodities contributing to dietary exposure are spinach, lettuce, and cabbage based on total exposure across the population. Around the 99th percentile, the same three dominated, but lettuce is most important (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0022).

The key residential exposure variables (based on Sobol sensitivity analysis; http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0023; slide 42) for this permethrin case study are: usage frequency for crack and crevice aerosol, surface-to-skin transfer efficiency, usage frequency for crack and crevice liquid, usage frequency for indoor fogger, and hand mouthing frequency.

Modeled Permethrin Exposure Uncertainty Analyses

Figure 3a shows the uncertainty for 3 CDFs based on bootstrap sampling of 50% of PDP cis-permethrin residues and 20%, 50%, 80% of the NHANES food consumption data (we used the 99th percentile as an indicator). It presents uncertainty results for daily dietary *cis*-permethrin exposure, based on bootstrapping 100 times. The three lines represent three sampling schemes: the blue line for 50% of residues and 20% consumption data; the pink line for 50% of residues and 50% residue data; and the black line for 50% residues and 80% consumption data. The CDF for the 50% of residues and 20% of consumption data has the biggest uncertainty. The ratio of the 97.5th percentile to the 2.5th percentile (95% confidence interval) is 15.07/4.63=3.3, reflecting the 97.5th/2.5th percentile ratio for an uncertainty run that used subsets: 50% *cis*-permethrin residue by raw agricultural commodity (RAC), and 20% of NHANES dietary consumption data for 3-5 year old children. In the same way, we calculated similar ratios for other bootstrapping schemes to evaluate the major factors contributing to the overall uncertainty (**Figure 3b**). As the sampling rate of consumption data increases, the ratio decreases until it reaches a plateau at about 60%, but there is no apparent pattern for residue data. Therefore, these uncertainty analyses show we have sufficient consumption data. However, more research is needed on residue uncertainty analyses. See Xue et al., 2010b, section 2.7 for more details.

Residential exposure uncertainty analysis results show that the 97.5th and 2.5th percentiles of the 99th percentile total dose permethrin profile are 119.5 and 17.2 with a ratio of 17 (FIFRA SAP, 2010 ; http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2010-0383-0023; slide 43). The ratio of the 97.5th to 2.5th percentile of the 95th percentile total dose profile is 6. The ratio of the 97.5th to 2.5th percentile of the 75th percentile total dose profile is 20. Thus, with current inputs, the 75th, 95th and 99th percentile uncertainty ratios are ~20, 6, and 17, respectively (from parameter uncertainty). See Glen et al., 2010, section 6.2, for more details.

DISCUSSION

Real-world data are needed for model inputs, and to evaluate model estimates. For example, biological measurements, in combination with other multimedia measurements and supporting information, may be used to estimate aggregate and cumulative exposures and doses, and compare to model predictions. Recent research efforts have collected critical data on potential exposures of young children (<6 years of age) in their homes and child care centers to the current-use pyrethroid pesticides (Morgan et al., 2007; Tulve et al., 2006, 2008). Applying SHEDS to estimate urinary 3-PBA concentrations resulted in a mean and 95th percentile of 0.8 and 3 µg/L; the estimated aggregate absorbed dose of permethrin accounted for approximately 50% of the urinary 3-PBA (Figure 2). These modeled estimates compare well with measured results reported from an observational pilot study of 127 young children in Ohio (Morgan et al., 2007). The mean and 95th percentile for measured urinary 3-PBA concentrations were 0.9 and 1.9 µg/L, respectively, and the authors estimated that the aggregate absorbed doses of permethrin accounted for about 60% of the excreted amounts of 3-PBA found in the children's urine (Morgan et al., 2007). (PBA is a common metabolite of several pyrethroid compounds.)

Using Tulve et al. (2008) multimedia measurement data as inputs to SHEDS, we compared the measured and predicted urinary 3-PBA metabolite concentrations to further evaluate the ability of SHEDS to estimate urinary 3-PBA concentrations (Tulve et al., 2011). In general, the modeled urinary concentrations compared well with the measured concentrations from this study, also. SHEDS accurately estimated both the high and low urinary 3-PBA concentrations found in the children's urine samples (Tulve et al., 2011).

As presented in the Results section, SHEDS dietary exposure estimates compared well at upper percentiles to the CTEPP duplicate diet data, and SHEDS aggregate (residential + dietary) dose estimates of 3-PBA compared well to the measured NHANES biomarker data at upper percentiles. The lower percentiles (p5 and p25) for SHEDS model estimates in Table 2 are orders of magnitude lower than CTEPP measurements because we used zeroes for non-detect values in SHEDS permethrin residue inputs. In the future, we will use pesticide usage information and detection limits to fill in non-detects, which should yield closer exposure results at lower percentiles; in this paper we focus on higher percentiles. We attribute the higher NHANES concentrations of urinary 3-PBA than SHEDS modeled estimates at lower percentiles to other pyrethroid pesticides besides permethrin. In addition, comparison of linked SHEDS-PBPK modeled estimates to the NHANES *cis*- and *trans*-DCCA data showed good agreement at upper percentiles (FIFRA SAP, 2010; http://www.epa.gov/heasd/products/sheds_multimedia/files/SHEDS%20PBPK%20Permethrin%20Case%20Study.pdf). These simulations suggest that permethrin accounts for approximately 50% of the *cis*- and *trans*-DCCA measured in the urine of the NHANES participants at the 75th percentile, and approximately 90% of the *cis*- and *trans*-DCCA at the 95th percentile. Such results suggests that permethrin exposure accounts for the higher exposures among pyrethroids bearing a DCCA moiety (i.e., cypermethrin, cyfluthrin, and permethrin). This finding is consistent with what is known for real-world dietary and residential/daycare exposures to these three pyrethroids (Tulve et al., 2006, 2008; Morgan et al., 2007, Stout et al., 2009b). A cumulative pyrethroids assessment is needed to determine the contribution of other pyrethroid pesticides to the cis- and trans-DCCA levels and 3-PBA levels found in urine samples.

The SHEDS modeling assessment in this paper reveals that, considering all homes (i.e., with and without permethrin use) the dietary pathway contributes the most to exposure for 3-5 year-old children, followed by non-dietary ingestion, inhalation, and dermal routes. This finding of relative pathway contribution is consistent with the CTEPP OH study (Morgan et al., 2007). SHEDS modeled dermal exposures could be under-predicting based on low skin residue loadings and use of a dermal absorption fraction (Kissel, 2011); future SHEDS research could adjust the absorption rate as a function of skin loading. Considering only children in homes with residential permethrin use, non-dietary ingestion was found to be more important than dietary and the other routes. The most important food commodities for dietary exposure were found to be lettuce, spinach, and cabbage. Uncertainty analyses show we have sufficient food consumption data for the SHEDS-Dietary module, but more research is needed on residue uncertainty analyses. Uncertainty for the residential module is much greater than for the dietary module. We believe this is due to the greater number of inputs needed for residential exposure modeling, especially for those key variables shown in the sensitivity analyses that are lacking data. These include surface-to-skin transfer efficiency, fraction of hand mouthed, saliva removal efficiency, hand-mouthing frequency, fraction of house treated, and usage frequency. More data collection of these inputs (e.g., updated usage information, mouthing frequencies for different lifestages) would be helpful for refined model estimates.

The focus of SHEDS is exposure, but the model does include a simple PK dose module. Ongoing research involves linking SHEDS exposure time series results with class-oriented PBPK models (FIFRA SAP, 2007) that estimate tissue burden and urinary concentrations, and tissue-based relative potency factors. The results from the linked models (i.e., outputs from SHEDS used as inputs to external PBPK models), various measurement studies, and corresponding data analyses will be used to quantify the cumulative exposure, dose, and risks to populations from pyrethroid mixtures in real-world scenarios. Initial dose estimates with the SHEDS-PK model, and linking SHEDS to a prototype PBPK dose model, have been tested using annual simulations of exposure (by pathway and aggregate) for single chemicals, including permethrin (FIFRA SAP, 2010). Specific plans for applying SHEDS for a cumulative pyrethroids assessment will include linking it with PBPK pyrethroid dose models, apportioning dietary and residential pathways, and considering the relative contribution of permethrin, cypermethrin and cyfluthrin to exposure and dose. Further testing of the linkages along with additional model evaluation using NHANES and measurement study data is underway and planned for a combined assessment of these three pyrethroids.

Additional future research activities and planned model refinements include the following: refine algorithms as needed to accommodate new research and regulatory applications; possible incorporation of source-to-concentration module (e.g., fugacity); enhance residential/dietary merging algorithms; refine to allow estimates at local (e.g., census tract) level; and improve cumulative algorithms. More longitudinal activity data from measurement studies are needed for evaluating and refining the D&A method to simulate longitudinal consumption and residential activity patterns, used in these SHEDS analyses. Future modeling efforts could incorporate other pathways; for example, food preparation and handling could contribute to exposures of children who have frequent mouthing behavior in a permethrin-contaminated residential environment. Future case studies may consider different populations, lifestages, chemicals/chemical classes or mixtures, seasons, and regions, and will include PBPK linkage, sensitivity and uncertainty analyses, and further model evaluations. Through these applications of the model, identification of key factors and data gaps will inform future data collection efforts. The methods and models developed through integrated modeling and measurements research will provide new insights and data that will inform and support aggregate and cumulative risk assessments for pyrethroids and other chemical classes.

Conclusions

This paper presents an aggregate permethrin exposure and dose assessment for 3-5 year-old children, using EPA's probabilistic SHEDS-Multimedia model. Close comparison of model estimates against measured duplicate diet and biomarker data provided multifaceted evaluation of the SHEDS algorithms and approaches used. Through model sensitivity and uncertainty analyses, we identified key factors and research needs to inform exposure measurement researchers and environmental health decision-makers. Collecting data for key inputs, such as consumption of specific commodities, surface-to-skin transfer efficiency, hand mouthing frequency, fraction of hand mouthed, saliva removal efficiency, fraction of house treated, and residential pesticide usage frequency, will reduce uncertainty for enhancing SHEDS model predictions in future applications. We conclude that the case study presented in this paper provides insights into children's residential and dietary exposures to the insecticide permethrin, illustrates the SHEDS aggregate exposure modeling methodology, and lays the foundation for a future cumulative pyrethroid pesticides risk assessment.

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FIGURE LEGENDS

Figure 1. Average contribution to total permethrin absorbed dose by pathway (3-5 year olds)

Figure 2. Comparison of 3-PBA in urine from NHANES and SHEDS from permethrin

Figure 3. SHEDS uncertainty analyses for dietary permethrin exposure (3-5 year olds)