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METHODOLOGIES FOR ESTIMATING CUMULATIVE HUMAN EXPOSURES TO CURRENT-USE PYRETHROID PESTICIDES

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ABSTRACT

We estimated cumulative residential pesticide exposures for a group of nine young children (4-6 years) using three different methodologies developed by the U.S. Environmental Protection Agency and compared the results with estimates derived from measured urinary metabolite concentrations. The Standard Operating Procedures for Residential Exposure Assessment (SOPs) are intended to provide a screening level assessment to estimate exposure for regulatory purposes. Nonetheless, dermal exposure estimates were typically lower from the SOP (1-1,300 nmol/d) than from SHEDS (5-19,000 nmol/d) or any of the four different approaches for estimating dermal exposure using the *Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways (Draft Protocol)* (5-11,000 nmol/d). Indirect ingestion exposure estimates ranged from 0.02-21.5 nmol/d for the SOP, 0.5-188 nmol/d for SHEDS, and 0-3.38 nmol/d for the *Draft Protocol*. Estimates of total absorbed dose ranged from 3-37 nmol/d for the SOPs, 0.5-100 nmol/d for SHEDS, and 1-216 nmol/d for the *Draft Protocol*. The concentrations estimated using the *Draft Protocol* and SHEDS showed strong, positive relationships with the 3-phenoxybenzoic acid (3-PBA) metabolite measured in the children's urine samples (R^2=0.90 for the *Draft Protocol*; R^2=0.92 for SHEDS). Analysis of different approaches for estimating dermal exposure suggested that the approach assuming an even distribution of pesticide residue on the child's body was most reasonable. With all three methodologies providing reasonable estimates of exposure and dose, selection should depend on the available data and the objectives of the analysis. Further research would be useful to better understand how best to estimate dermal exposure for children and what exposure factors (e.g., activities, transfer coefficients, measurement techniques) are most relevant in making dermal exposure estimates.

INTRODUCTION

Young children's activities may increase their exposures to environmental chemicals. The U.S. Environmental Protection Agency's (EPA) Office of Research and Development (ORD) conducts research related to children's exposure and risk in support of Executive Order 13045 (http://www.epa.gov/fedrgstr/eo/eo13045.htm), the Food Quality Protection Act (FQPA) of 1996 (http://www.epa.gov/pesticides/regulating/laws/fqpa/), and the Safe Drinking Water Act Amendments of 1996 (http://www.epa.gov/safewater/sdwa/index.html). FQPA requires the EPA to consider in its risk assessment procedures the potential susceptibility of infants and children to both aggregate (e.g., multi-pathway) and cumulative (e.g., multi-chemical) exposures to pesticides.

In 2001, the EPA published the *Draft Protocol for Measuring Children's Non-Occupational Exposure to Pesticides by all Relevant Pathways* (hereafter "*Draft Protocol"*) which details a systematic measurement-based approach to evaluate exposure by each route (i.e., inhalation, dermal, ingestion) using a series of algorithms. Each algorithm mathematically expresses exposure for a specific route as a function of chemical concentration in different environmental media and selected exposure factors, explicitly identifying the data requirements. Typically, a complete dataset is needed to estimate aggregate exposures using these algorithms (US EPA, 2001).

Recent research efforts have collected much needed data to improve our understanding of the potential exposures of young children in their everyday environments (Morgan *et al.*, 2005; Whyatt *et al*., 2004; Fenske *et al*., 2005; Lu *et al*., 2006; Bradman *et al.*, 2007; Tulve *et al*., 2008). However, few studies have used a systematic data collection approach (Cohen Hubal *et al.*, 2000a, b) to collect the multimedia samples and activity pattern information necessary to

estimate a young child's aggregate exposures to pesticides. Often, researchers have collected environmental, biological, or personal exposure measurements and ancillary questionnaire information using non-standardized methods or protocols, while others have produced exposure estimates for young children that rely heavily on default data inputs.

In conducting pesticide risk assessments, EPA also considers available information concerning the cumulative effects on human health resulting from exposure to multiple chemicals that have a common mechanism of toxicity. An important consideration in estimating cumulative risks to pesticides is how to combine pesticides with different potencies and exposure characteristics (Wilkinson *et al.*, 2000). Various approaches include the use of a hazard index, reference point index, toxicity equivalence factors, relative potency factors, combined margin of exposure procedures, point of departure index, the cumulative risk index, combined mechanism of toxicity, and physiologically-based toxicokinetic modeling (Wilkinson *et al.*, 2000; Boobis *et al.*, 2008; http://www.epa.gov/pesticides/cumulative/rra-op/). Often, data inputs for cumulative exposure estimates are derived from pre-existing data sources (e.g., residue databases, food consumption surveys) or default parameters (e.g., Exposure Factors Handbook) which may or may not be appropriate to the population of interest.

For several years, EPA researchers have been evaluating the data requirements for assessing aggregate exposure and cumulative risk in field and laboratory studies. One such field study was collaboratively conducted by the EPA, the Centers for Disease Control and Prevention (CDC), and the Duval County Health Department, FL (DCHD). The overarching goal was to evaluate young children's potential exposures to current-use pesticides in their residential environment. Details and selected results have been published previously, including the multimedia measurements and activity pattern information (Tulve *et al.*, 2008) and the

biomonitoring data (Naeher *et al.*, 2010). Here, we estimate the cumulative exposures to pesticides for nine children using available tools, including measurements (Tulve *et al*., 2008), the *Draft Protocol* (US EPA, 2001), the Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multipathway Pollutants (SHEDS; Zartarian *et al*., 2000, 2008), and EPA's Office of Pesticide Programs' (OPP) Standard Operating Procedures (SOPs) for Residential Exposure Assessments (US EPA, 1997).

The objectives of this manuscript are to 1) use a complete dataset (i.e., environmental and biological measurements, activity information) collected in an observational exposure study to evaluate the *Draft Protocol* for estimating potential cumulative exposures to the current-use residential pyrethroid pesticides, 2) compare the cumulative exposure estimates calculated from the *Draft Protocol* with estimates from SHEDS and SOPs, and 3) compare the urinary biomarker measurements with estimates generated from the *Draft Protocol*, SHEDS, and SOPs.

MATERIALS AND METHODS

Pilot Observational Exposure Study

Nine children (4 to 6 years) and their caregivers participated in a pilot study in which residential multimedia measurements (indoor and outdoor air, socks, application and play area surface wipes, food, urine) and activity pattern data were collected for one 24-hour period to assess potential exposures to residential pyrethroid pesticides (Tulve *et al.*, 2008). This was an observational research study, as defined in 40 CFR Part 26.402. The study protocol and procedures to obtain the assent of the children and informed consent of their parents or guardians were reviewed and approved by three independent institutional review boards and complied with

all applicable requirements of the Common Rule regarding additional protections for children (Subpart D).

Cumulative Exposure Methods

Cumulative exposure estimates combine aggregate exposure estimates for all chemicals with a common mode of action. All pyrethroid pesticides that metabolize to 3-PBA were considered for this evaluation. Information on the multimedia measurements (Tulve *et al.*, 2008), multi-residue analysis method (Tulve *et al.*, 2006), and child-specific inhalation rates (Table S1) are provided in the supplementary information. A summary of the input parameters is provided in Table 1. The molar concentrations are the sum of the detected pesticides. Exposure factors needed for calculations were taken from the Child-Specific Exposure Factors Handbook (US EPA, 2002), CDC standard reference curves (Ogden *et al*., 2002), the *Draft Protocol* (US EPA, 2001), and the peer-reviewed literature. Child-specific age, sex, and activity information were used.

Draft Protocol

The *Draft Protocol* details a systematic measurement-based approach to evaluate exposure by the inhalation, dermal, and ingestion routes of exposure (US EPA, 2001). All location information, activity levels, durations, and clothing coverage are gleaned from the child-specific time activity diaries.

Aggregate Exposure

Aggregate exposure is defined as the exposure from all sources, routes, and pathways for individual pesticides (equation 1).

$$E_{aggregate} = E_i + E_d + E_{ii} + E_f \qquad \text{(equation 1)}$$

where aggregate exposure ($E_{aggregate}$) is the sum of the exposures from the inhalation (E_i), dermal (E_d), indirect ingestion (E_{ii}), and dietary (E_f) routes in a 24 hr period. Modifications to the *Draft Protocol* algorithms were made where necessary for applicability to the samples collected in the pilot study. The reader is referred to the report (US EPA, 2001) for the original equations.

Inhalation Exposure

The inhalation exposure route is described in equation 2:

$$E_i = \sum (C_{me})(T_{ma})(IR_{ma}) \qquad \text{(equation 2)}$$

where E_i = sum of the inhalation exposures for all microenvironments and activity levels (nmol/d), C = air concentration (nmol/m^3), *me* = microenvironment, T = activity time (hr/d), *ma* = activity level (sleeping/napping, quiet, or active play), and IR = inhalation rate (m^3/hr).

Dermal Exposure

The equation depicting dermal exposure is described in equation 3:

$$E_d = \left(\sum (C_{sock})(SA_x)\right) \times (T) \qquad \text{(equation 3)}$$

where E_d = sum of the dermal exposures for all microenvironments and activity levels (nmol/d), C_{sock} = pesticide residue concentration on the socks (nmol/cm^2), SA_x = surface area of body part (cm^2), x = body parts exposed (feet, hands, arms, legs, trunk), T = indoor time awake (hr/d).

We used four different approaches for the dermal exposure algorithm: *uniform distribution, fractional loading from socks, hand*, and *apportioning*. All approaches limited exposure duration to time spent awake and indoors at home and assumed 1) body surface area was a function of age and sex, and, 2) clothing was a barrier preventing contact with the skin. In the *uniform distribution* approach, the pesticide residue loadings on the socks were used as a maximum estimate of the loadings on the rest of the body (excluding head and clothing covered areas) assuming an even distribution. In the *fractional loading* approach, we assumed that

158 pesticide residue loadings on the feet and hands equaled those on the socks and the loadings for
159 all other body parts were 13% of those on the socks based on measurements reported by Hore
160 (2003). The *hand* approach differs from the *fractional loading* approach only in that the
161 pesticide residue loadings on the hands was assumed to be equal to the pesticide residue loadings
162 measured on the play area surfaces. The *apportioning* approach enhances the hand approach
163 through the use of more expansive cotton garment data reported by Bradman *et al*. (2007), in
164 which the residue loading on young children's arms and legs were calculated to be 36% and
165 40%, respectively, of the residue loading on the feet.
166 *Indirect Ingestion Exposure*
167 Indirect ingestion is defined as the consumption of pesticide residues from any non-food
168 item that enters the mouth. For simplicity, we assumed that the hands were the predominant
169 contributor for these children. The indirect ingestion exposure route is described in equation 4:

170 $$E_{ii} = \sum (C_{hands})(TE)(SA)(EF)(T) \qquad \text{(equation 4)}$$

171 where E_{ii} = sum of the indirect ingestion exposures for all microenvironments and activity levels
172 (nmol/d), C_{hands} = pesticide residue concentration from the play area surface wipes (nmol/cm^2),
173 TE = transfer efficiency (unitless), assumed to be 0.5, SA = surface area of hands put in mouth
174 (cm^2/event), EF = frequency of mouthing events (events/hr), T = indoor quiet time (hr/d).
175 *Dietary Exposure*
176 Dietary exposure is based on the duplicate diet method for collection of food and
177 beverage samples in which duplicate portions of the foods eaten and liquids consumed are
178 collected and analyzed as composite samples. The dietary exposure route is described in
179 equation 5:

180 $$E_f = \sum (C_f)(W_f) \qquad \text{(equation 5)}$$

where E_f = sum of the dietary ingestion exposures (nmol/d), C_f = pesticide residue concentration in the duplicate diet sample (nmol/g), W_f = weight of food in the duplicate diet sample (g/d).

SHEDS

Briefly, SHEDS (Version 3) is a physically-based, probabilistic model that predicts, for user-specified population cohorts, exposures incurred via inhalation, dermal contact, and indirect ingestion of residues from hand- and object-to-mouth activities. It combines information on chemical usage, human activity/location data, environmental concentrations, and exposure factors to generate time series of exposure for simulated populations. One- or two-stage Monte Carlo simulation can be used to produce distributions of exposure for various population cohorts that reflect the variability and uncertainty in the input parameters (Zartarian *et al.*, 2008). SHEDS can be used to make exposure and dose estimates with a limited dataset based on assumed distributions for various model parameters. Detailed discussions of the SHEDS model are available in Zartarian *et al.* (2000, 2006, 2008) and Xue *et al*. (2006).

The multimedia measurements for each home (Table 1) and actual participant time activity/location profiles were used to generate time series of exposure for the inhalation, dermal, and hand-to-mouth exposure routes for the nine children. The remaining input parameters are presented in Table 2. Although a dietary module that uses recipe files, consumption data, and food residue data is available in SHEDS, we instead chose to use pesticide residue concentrations (Table 1) measured in the duplicate diets to estimate ingested mass through the dietary route of exposure.

Office of Pesticide Programs Residential SOPs (SOPs)

The Office of Pesticide Programs (OPP) uses a set of standard operating procedures (SOPs) to estimate post-application exposures for toddlers from dermal contact and hand-to-

mouth activity from residential surfaces that have been treated with pesticides (US EPA, 1997). These SOPs are used for product registration or re-registration in the United States and are intended to provide a screening level assessment to estimate exposures when data are limited and exposure estimates beyond the day of application are desired. The registered use pattern (e.g., broadcast or crack and crevice) of the product is used to determine the pesticide residue distribution in the residence and length of time the pesticide residues are available for exposure. To ensure that the highest residue concentrations are available for exposure, pesticide residues based on maximum application rates are typically used. For this evaluation, however, the data in Table 1 were used as inputs for the exposure estimates, recognizing that they likely were not measured immediately following a pesticide application, the applications were targeted applications, and the pesticide residues were not uniformly distributed in the residence.

Dermal Exposure

The dermal exposure algorithm is presented in equation 6.

$$E_d = (ISR)(TC)(ET) \qquad \text{(equation 6)}$$

where E_d = dermal exposure (nmol/d), ISR = pesticide residue concentration on the play area surface wipes (nmol/cm^2), TC = transfer coefficient (cm^2/hr), assumed to be 6000 cm^2/hr for a 15 kg child (US EPA, 1999), ET = indoor time awake (hr/d).

Indirect Ingestion Exposure

Indirect ingestion of pesticide residues is calculated using equation 7.

$$E_{ii} = (ISR)(SA)(FQ)(ET) \qquad \text{(equation 7)}$$

where E_{ii} = indirect ingestion exposure (nmol/d), ISR = pesticide residue concentration on the play area surface wipes (nmol/cm^2), SA = surface area of hand that contacts the mouth

(cm^2/event), assumed to be 20 cm^2/event (US EPA, 1999), *FQ* = frequency of hand-to-mouth events (events/hr), assumed to be 20 events/hr (US EPA, 1999), *ET* = indoor quiet time (hr/d).

Inhalation Exposure

While an SOP does exist to estimate post-application inhalation exposures, it is typically only used when a chemical's physicochemical properties would suggest a high enough vapor pressure that the active ingredient would be in the air after application. For the current-use pyrethroid pesticides, OPP considers inhalation exposures negligible, since, with few exceptions, their vapor pressures are less than 1 x 10^{-6} mm Hg (US EPA, 2009).

OPP does not have a residential SOP to estimate dietary exposures and routinely uses the probabilistic Dietary Exposure Evaluation Model (DEEM) for dietary exposure estimates (http://www.epa.gov/pesticides/science/models_pg.htm). For this manuscript we estimated the dietary route from what was measured in the duplicate diet instead of predicting the dietary exposures using DEEM.

Estimating Dose

The exposure data provide an estimate of how much chemical the child may have come into contact with during a single day. Applying literature-derived absorption factors, we can estimate absorbed dose. Human absorption data values (16% inhalation; 2% dermal; 53% ingestion; 64% of parent pesticide excreted in urine as 3-PBA on a molar basis) are available in the scientific literature for cypermethrin and cyfluthrin (Leng *et al*., 1997; Woollen *et al*., 1992; Eadsforth *et al*., 1988; Eadsforth and Baldwin, 1983). These absorption factors were also applied to the remaining pyrethroids to estimate absorbed dose and urinary metabolite concentrations.

249 RESULTS AND DISCUSSION

250 The relationship between the multimedia measurements and the measured urinary 3-PBA
251 metabolite concentrations was evaluated using a linear regression analysis. A strong, positive
252 relationship was determined between the measured urinary 3-PBA metabolite concentrations and
253 the sock data (R^2=0.95, p<0.0001), while weaker relationships were determined for the indoor air
254 (R^2=0.35, p=0.09), application area surface wipe (R^2=0.33, p=0.1), outdoor air (R^2=0.15, p>0.1),
255 play area surface wipe (R^2=0.08, p>0.1), food (R^2=0.02, p>0.5). These analyses suggested that
256 the sock samples, rather than the surface wipe samples, were more appropriate to use to estimate
257 dermal exposures.

258 Inhalation exposures estimated using the *Draft Protocol* ranged from 0.04-2.0 nmol/d,
259 with similar values estimated using SHEDS (0.07-2.1 nmol/d) (Table 3). The low inhalation
260 exposure estimates calculated with the *Draft Protocol* and SHEDS support OPP's supposition
261 that post-application inhalation exposures for low vapor pressure pesticides can be considered
262 negligible.

263 The amount of spatial variability in surface pesticide residue concentrations within each
264 home (Table 1) suggests that dermal exposure estimates based on surface wipes may contain
265 substantial measurement error. Residues measured on the sock samples may be more
266 representative of the average transferable pesticide residues that the child came in contact with
267 during normal activities in the home, and are thus more appropriate to use for estimating dermal
268 exposures for this age group. Cotton garments have been used successfully for estimating
269 dermal exposure to pyrethroid pesticides in the past (Cohen Hubal *et al.* 2006).

270 The dermal exposure estimates are shown in Table 4. The four different approaches from
271 the *Draft Protocol* produced results ranging from 8-11,000 nmol/d for the *uniform distribution*

approach; 8-4,500 nmol/d for the *fractional loading from socks* approach; 5-2,400 nmol/d for the *hand* approach; and 6-3,000 nmol/d for the *apportioning* approach. The SHEDS dermal exposure estimates ranged from 5-19,000 nmol/d, while the SOP estimates ranged from 1-1,300 nmol/d. The SHEDS dermal exposure estimates are most similar to the dermal exposure estimates using the *Draft Protocol* with the uniform distribution approach. Also, the SOP estimates are most similar to the hand and apportioning approaches which included the measured play area surface wipes. While the rank order of the participants in regards to their dermal exposure estimates varied for the lowest dermal exposure estimates, some consistency was evident among the highest estimates. Specifically, Participants 3, 4, and 5 occupied the highest ranks (7 through 9) for all *Draft Protocol* and SHEDS estimates. The range of SOP dermal exposure estimates is smaller than either the *Draft Protocol* or SHEDS. The highest dermal exposure estimates resulted from SHEDS, despite the inclusion of hand washing and bathing events.

We further evaluated whether the surface wipe or sock samples were more appropriate for estimating dermal exposures. Using SHEDS, we calculated the dermal exposure using the average of the surface wipe concentrations (data in Table 1) and transfer coefficients from Cohen Hubal *et al*. (2006) (original data fit to a lognormal distribution). We then compared these dermal exposure estimates with those calculated using the sock samples. The dermal exposure estimates using the sock samples compared more favorably with the measured urinary 3-PBA metabolite concentrations than did the estimates based on surface wipe samples (data not shown).

We also used sock data to estimate dermal exposure using the SOP. With the sock data, the SOP dermal exposure estimates ranged from 83-29,000 nmol/d, with Participants 3, 4, and 5

295 occupying the highest ranks when rank ordered (data not shown). These values are consistent
296 with the dermal exposure estimates using the *Draft Protocol* with the uniform distribution
297 approach and SHEDS dermal exposure estimates, suggesting that the data input used is important
298 in estimating exposure. With the exception of Participant 9, the pesticide residues measured on
299 the socks are larger than the pesticide residues measured on the play area surface wipes;
300 therefore, it is reasonable to assume that the dermal exposure estimates would be larger when the
301 sock data were used. The pesticide residues on the socks may be more appropriate to use for
302 estimating dermal exposure when evaluating young children's exposures to pesticide residues
303 found in their everyday environments since the sock may be more representative of the pesticide
304 residues where the child has spent time as compared to the play area surface wipe. More
305 research is needed to evaluate the applicability of a cotton garment (such as the socks) to
306 estimate dermal exposures for children in different age and developmental stages and to
307 understand what the residues on the cotton garment may represent.

308 Understanding the relationship between a cotton garment and a sample used to collect a
309 surface pesticide residue (e.g., wipe, roller, surface press sampler, vacuum) is critical for
310 evaluating children's dermal exposure estimates. The disparity in the results from the different
311 methodologies suggests that further research would improve our understanding of how best to
312 estimate dermal exposure for children, what exposure factors (e.g., activities, transfer
313 coefficients, cotton garments, total residue, transferable residue, dust-bound residue, cleaning
314 practices, hygiene) are most relevant in making dermal exposure estimates, how dust-bound
315 residues impact transfer and absorption factors, and how dermal exposures relate to urinary
316 biomarker concentrations. Adequate information on the measurement methods and the factors
317 that reduce the uncertainty in the dermal exposure estimates are needed.

318 Table 5 shows the ingestion exposure estimates with the results for indirect ingestion
319 ranging from 0-3.38 nmol/d for the *Draft Protocol*, 0.5-188 nmol/d for SHEDS, and 0.02-21.5
320 nmol/d for the SOP. Participant 9 had the highest exposure estimate calculated from the *Draft*
321 *Protocol* and SOP, whereas with SHEDS, Participant 5 had the highest estimate. For the *Draft*
322 *Protocol*, we estimated the indirect ingestion exposure using the following data: the play area
323 surface wipe represented the loading on the hands, the transfer efficiency was assumed to be 0.5
324 (California EPA estimate), and the mouthing time for quiet, indoor hours was taken from the
325 time activity diary. Literature-derived values were used for the surface area of the hand that was
326 mouthed and the number of mouthing events per hour (Tulve *et al.*, 2002; US EPA, 1999, 1997).
327 SHEDS and the SOP used slightly different data inputs.
328 One question asked of the caregivers was whether their children were known to put their
329 thumbs, fingers, or toes into their mouths. Two caregivers reported that their children
330 (Participants 4 and 6) did put their hands into their mouths. However, additional information on
331 amount of hand mouthed and the number of mouthing events in a time period were not captured.
332 One method to estimate indirect ingestion exposure requires the pesticide residue concentration
333 on the hands, transfer efficiency, surface area of the hands mouthed, and frequency of mouthing
334 events (US EPA, 2001). This data intensive method is likely to reduce the uncertainty in the
335 indirect ingestion exposure estimate. However, we did not collect any of this information since
336 it would have required field technician observations of each participant. SHEDS used literature-
337 derived distributions for estimating the frequency of hand-to-mouth behavior so that each
338 participant would have an indirect ingestion contribution (Xue *et al.*, 2007) (Table 2). Further
339 research is necessary to understand the exposure factors (e.g., objects mouthed, length of

mouthing, mouthing and activities) that accurately estimate indirect ingestion exposures since ingestion (both dietary and indirect) is an important route of exposure.

Table 5 also shows the dietary ingestion exposure estimate. The individual-level dietary information collected in this study made the population-level estimates in SHEDS and the SOP unnecessary. We assumed that the dietary ingestion exposure estimate calculated from the duplicate diet samples using the *Draft Protocol* was most representative of these participants actual dietary exposures.

Understanding the data inputs for a selected algorithm is very important. For this evaluation, most of the data were collected from one cohort participating in a pilot observational exposure study. Often, other data or exposure factors would need to be used as inputs to supplement what was collected in the field study. We (study authors) advocate caution when using available data (e.g., published and unpublished) since the sample collection methods, sample collection locations (e.g., residential, business), cohort (e.g., age, sex, occupation), quality assurance and control measures, and other variables may not be appropriate for the intended use of those data.

Using the *Draft Protocol*, the dose estimates ranged from 1-216 (*uniform distribution*), 1-91 (*fractional loading from socks*), 1-50 (*hand*), and 0.7-61 (*apportioning*) nmol/d for the four dermal approaches, while the SHEDS dose estimates ranged from 0.5-100 nmol/d and the SOPs dose estimates ranged from 3-37 nmol/d (Figure 1). The three methodologies did not consistently predict the highest or lowest absorbed doses. For both the *Draft Protocol* and SHEDS, the estimates of absorbed dose were highest for Participant 5. For the *Draft Protocol*, Participant 8 had the smallest absorbed dose, while for SHEDS Participant 9 had the smallest absorbed dose. Unlike the other methodologies, Participants 3 and 9 had the highest absorbed

363 doses and Participant 1 had the lowest absorbed dose when estimated from the SOPs. The
364 average dose is comparable for the *Draft Protocol* (56, 26, 16, 19 mol/d with the four dermal
365 approaches), SHEDS (30 nmol/d), and SOPs (15 nmol/d).
366 The estimated and measured urinary 3-PBA concentrations can be compared to determine
367 how well our systematic approach compares to the biological measurements. For all
368 comparisons, we used the measured urinary 3-PBA concentration as the correct concentration,
369 but acknowledge that measurement error is likely due to factors such as fluctuations in urine
370 volume, metabolite concentrations, and timing of sample collection. Figure 2 shows a
371 comparison of the calculated urinary 3-PBA concentrations and the concentrations measured in
372 the urine samples collected from the participants. In general, the concentrations estimated using
373 the *Draft Protocol,* SHEDS, and SOPs compare well with the measured concentrations.
374 However, it should be noted that there is no clear relationship between the ability of the
375 methodologies to over- or under-predict the measured urinary 3-PBA concentrations. However,
376 the methodologies appear capable of accurately estimating both the high and low urinary 3-PBA
377 concentration measurements found in the children's urine samples.
378 The agreement between the measured and estimated urinary 3-PBA concentrations are
379 evaluated with bias and 95% limits of agreement in Bland-Altman plots (Figure S1). The Bland-
380 Altman plots indicate that the uniform distribution approach and SHEDS offer the best
381 agreements with the measured values. However, further research is necessary to understand
382 whether a maximum pesticide residue concentration, such as what was used in the uniform
383 distribution approach or SHEDS, is a reasonable expectation for children's skin based on their
384 residential environments. Due to the small sample size, the increasing refinement of the
385 pesticide residues on different body parts in the other dermal approaches (*fractional loading*

386 *from socks, hand, apportioning*) may not improve the dermal exposure estimates even though,
387 intuitively, these estimates are more reasonable. For example, with activities involving sitting,
388 standing, or kneeling and removal processes such as hand washing, it is reasonable to believe
389 that different parts of the body would have different pesticide residue concentrations.
390 The relationship between the estimated and measured metabolite concentrations was also
391 evaluated using a linear regression analysis. A positive relationship was determined for
392 estimated and measured urinary 3-PBA concentrations (R^2=0.90 for the *Draft Protocol* with each
393 dermal approach; R^2=0.92 for SHEDS; R^2=0.13 for the SOPs), suggesting that any of the
394 methodologies can be used to derive a urine concentration that is predictive of what was
395 measured in the urine for this dataset. Understanding the applicability to other populations is
396 limited due to the small sample size and single location. These results suggest that our
397 systematic data collection approach to collect environmental, biological, personal, and activity
398 pattern data to estimate young children's aggregate and cumulative exposure and dose to
399 pesticides is reasonable. However, there are certain considerations, including assuring that the
400 data were systematically collected, the urine sample was accurately collected, any assumptions
401 used in each methodology were reasonable, and consideration is given for how to account for all
402 potential exposures (e.g., locations in addition to home).
403 The agreement between the measured metabolite concentrations and each methodology
404 for estimating exposure was further evaluated using the intraclass correlation coefficient (ICC).
405 A high ICC denotes consistency between the methodologies. With an ICC of 0.93, agreement
406 was greatest between the measured metabolite concentrations and the *Draft Protocol* with the
407 uniform distribution approach. The ICCs were 0.79 with SHEDS and 0.72 with the *Draft*
408 *Protocol* with the fractional loading from socks approach. All other agreements were poor, with

ICCs of 0.50 or less. These observations suggest that the metabolite concentrations estimated using the *Draft Protocol* with the uniform distribution or fractional loading from socks approaches and SHEDS are more consistent with the measured urinary metabolite concentrations than are the other methodologies.

The dose estimate information can also be used to calculate the relative contributions from each exposure route. For the *Draft Protocol* with each dermal approach, pathway contributions were estimated for each participant (primary contributing exposure route in parentheses). For Participants 1 (77%), 2 (77%), and 6 (94%), diet was the primary contribution to the dose estimate; for Participants 3 (90%), 4 (99%), 5 (99%), 7 (92%), and 8 (55%), dermal was the primary contribution to the dose estimate; and for Participant 9 (78%) indirect ingestion was the primary contributor to the dose estimate when using the *Draft Protocol* with the uniform distribution approach. Pathway contributions using the *Draft Protocol* with the fractional loading from socks, hand, and apportioning approaches are discussed in the supplementary information. Regardless of the dermal approach used in the *Draft Protocol* calculations, four children had dermal as their major pathway for pesticide exposure, four children had dietary as their major pathway for exposure, and one child either had indirect ingestion or dermal as the major exposure pathway.

Similar analyses were completed for the results generated by SHEDS and SOPs (see supplementary information for details). The *Draft Protocol*, SHEDS, and SOPs calculated the primary contributor to the dose estimate to be the same for Participants 1, 2, and 6 (diet) and Participants 3, 4, 5, and 7 (dermal) even with small differences in the data inputs, assumptions, and overall methodologies.

The data suggest that the most highly exposed children, based on urine measurements and predicted dose, had dermal as the primary route of exposure. Inhalation exposure was negligible in contributing to the dose estimates for any of the methodologies. While the results presented in this paper are encouraging, over-interpretation of the results is discouraged because of the small sample size and one study location used for the evaluation.

In summary, we have shown that a systematic data collection approach can be used to estimate young children's exposure to pesticides in their residential environments. The *Draft Protocol* with the four dermal approaches and SHEDS predict that diet is the primary exposure pathway for Participants 1, 2, and 6 and dermal for Participants 3, 4, 5, and 7. Indirect ingestion and inhalation were less important routes of exposure for the pyrethroids for this small sample of children in one study in one location over one 24-hr time period. Limitations of the study results include a small sample size in one location, exposure factors derived from literature sources, variations in inputs and assumptions, and uncertainty on how best to estimate dermal and indirect ingestion exposures. Although there are limitations to the study, these findings are important in focusing future research efforts on important exposure factors for young children. If dermal and dietary are the most important routes of exposure, then more research is necessary to understand how to best collect and use dermal exposure information. Few research studies allow us to understand how much pesticide residue is on various parts of the body. Bradman *et al*. (2007) and Hore (2003) provide a preliminary understanding, but further research would be useful to understand what parts of the body are most highly exposed, activities that influence exposures, relationships of the loadings on various body parts to each other, and whether dermal exposure alone can be used to predict urine concentrations. We have shown that all three methodologies

453 are reasonable for estimating exposure and dose, however, the available data and the
454 interpretation of the results may influence the method used.
455
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595 arsenic exposure assessment for children who contact CCA-treated playsets and decks, part 1:
596 model methodology, variability results, and model evaluation. *Risk Anal* 2006; **26**(2): 515-31.

597 Table 1. Input parameters for the *Draft Protocol* and SOPs summarized from Tulve *et al*. (2008).

Multimedia Concentrations							
Home	Pesticides[a]	Indoor Air ($nmol/m^3$)	Outdoor Air ($nmol/m^3$)	Wipe, Appl Area ($nmol/cm^2$)	Wipe, Play Area ($nmol/cm^2$)	Sock ($nmol/cm^2$)	Food (nmol/g)
1	*cis/trans*-Permethrin, Cypermethrin	0.01	0.02	0.001	0.00003	0.002	0.01
2	*cis/trans*-Permethrin, Cypermethrin, Delta/Tralomethrin, Esfenvalerate, *lambda*-Cyhalothrin	0.02	0.02	0.03	0.0003	0.02	0.1
3	*cis/trans*-Permethrin, Cypermethrin, Delta/Tralomethrin, Esfenvalerate	0.2	0.1	1.4	0.1	0.4	0.04
4	*cis/trans*-Permethrin, Cypermethrin, Delta/Tralomethrin, Esfenvalerate, Sumithrin	0.6	0.01	0.4	0.01	0.6	0
5	*cis/trans*-Permethrin, Cypermethrin	0.3	0.02	0.5	0.02	1.0	0.01
6	*cis/trans*-Permethrin, Cypermethrin, *lambda*-Cyhalothrin, Sumithrin	0.01	0.01	0.01	0.01	0.02	0.02
7	*cis/trans*-Permethrin, Cypermethrin, Sumithrin	0.01	0.01	0.01	0.002	0.02	0.002
8	*cis/trans*-Permethrin, Cypermethrin,	0.01	0.01	0.2	0.01	0.02	0.01

	Sumithrin						
9	*cis/trans*-Permethrin, Cypermethrin, Delta/Tralomethrin, Esfenvalerate	0.03	0.01	0.2	0.1	0.004	0.003
Time Activity Information							
Participant	Age (yrs), Sex, Weight[b] (kg)	Sleeping/Napping (hr)	Indoor Quiet (hr)	Indoor Active (hr)	Outdoor Quiet (hr)	Outdoor Active (hr)	Away from Home (hr)
1	6, Male, 21	14	4.5	4.5	0	0.5	0.5
2	4, Male, 16	10	1	1.5	1.5	1	9
3	6, Male, 21	9.5	0	4	0	1	9.5
4	6, Female, 20	11	3	2	0	0.5	7.5
5	4, Female, 16	12.5	2.5	2.5	0	6.5	0
6	5, Male, 18	11	0.75	0.75	1	3	7.5
7	4, Female, 16	10.5	5.5	5.5	1	1.5	0
8	5, Female, 18	11	1	3	0.5	0.5	8
9	6, Male, 21	12.5	1.75	1.75	0	0.5	7.5

598 [a]Pesticides listed here degrade to 3-PBA and were measured in the collected samples for a home.

599 [b]Median weight values from CDC standard reference curves (Ogden *et al.*, 2002).

600 Table 2. Input parameters for SHEDS.

Input Parameter	Distribution Type	Parameter Estimate[a]		Units	Reference
		ν_1	ν_2		
Hand washing events per day	Point	-	-	Events/d	Directly from time activity diary
Hand washing removal efficiency	Uniform	0.5	1.0	Fraction	Zartarian *et al.*, 2000
Bathing events per day	Point	-	-	Events/d	Directly from time activity diary
Bathing removal efficiency	Uniform	0.5	1.0	Fraction	Zartarian *et al.*, 2000
Maximum dermal loading hands	Point	3.0	-	nmol/cm^2	3 times maximum sock loading
Maximum dermal loading body	Point	3.0	-	nmol/cm^2	3 times maximum sock loading
Fraction of hands with residue going to mouth	Beta	3.7	25	Fraction	Zartarian *et al.*, 2000 Table 10
Frequency of hand-to-mouth activity	Weibull	0.7	10.2	Number per hour	Xue *et al.*, 2007
Saliva removal efficiency	Uniform	0.1	0.5	Fraction	Zartarian *et al.*, 2000

601 [a]Distributional parameters (ν_1, ν_2): Uniform (minimum, maximum); Beta (shape 1, shape 2); Weibull (shape, scale).

602 Table 3. Inhalation exposure estimates calculated from each method.

Participant ID	Inhalation Exposure Estimate using *Draft Protocol* (nmol/d)	Inhalation Exposure Estimate from SHEDS (nmol/d)	Inhalation Exposure Estimate from SOP[a] (nmol/d)
1	0.1	0.1	-
2	0.1	0.1	-
3	0.8	1.0	-
4	2.0	2.1	-
5	1.0	1.6	-
6	0.05	0.07	-
7	0.1	0.1	-
8	0.04	0.07	-
9	0.1	0.1	-

603 [a]Inhalation exposure estimates are negligible for the current-use pyrethroid pesticides. See text for details.

604 Table 4. Dermal exposure estimates calculated from each method.

Participant ID	Dermal Exposure Estimate using *Uniform Distribution* Approach – *Draft Protocol* (nmol/d)	Dermal Exposure Estimate using *Fractional Loading from Socks* Approach – *Draft Protocol* (nmol/d)	Dermal Exposure Estimate using *Hand* Approach – *Draft Protocol* (nmol/d)	Dermal Exposure Estimate using *Apportioning* Approach – *Draft Protocol* (nmol/d)	Dermal Exposure Estimate from SHEDS (nmol/d)	Dermal Exposure Estimate from SOP (nmol/d)
1	37	15	8	10	54	1
2	120	48	26	32	200	5
3	4700	2000	1100	1400	6900	1300
4	7600	3100	1700	2100	11000	220
5	11000	4500	2400	3000	19000	730
6	21	11	5	6	30	64
7	420	170	100	130	740	160
8	28	28	10	10	21	160
9	8	8	88	88	5	1300

605 Table 5. Ingestion exposure estimates calculated from each method.

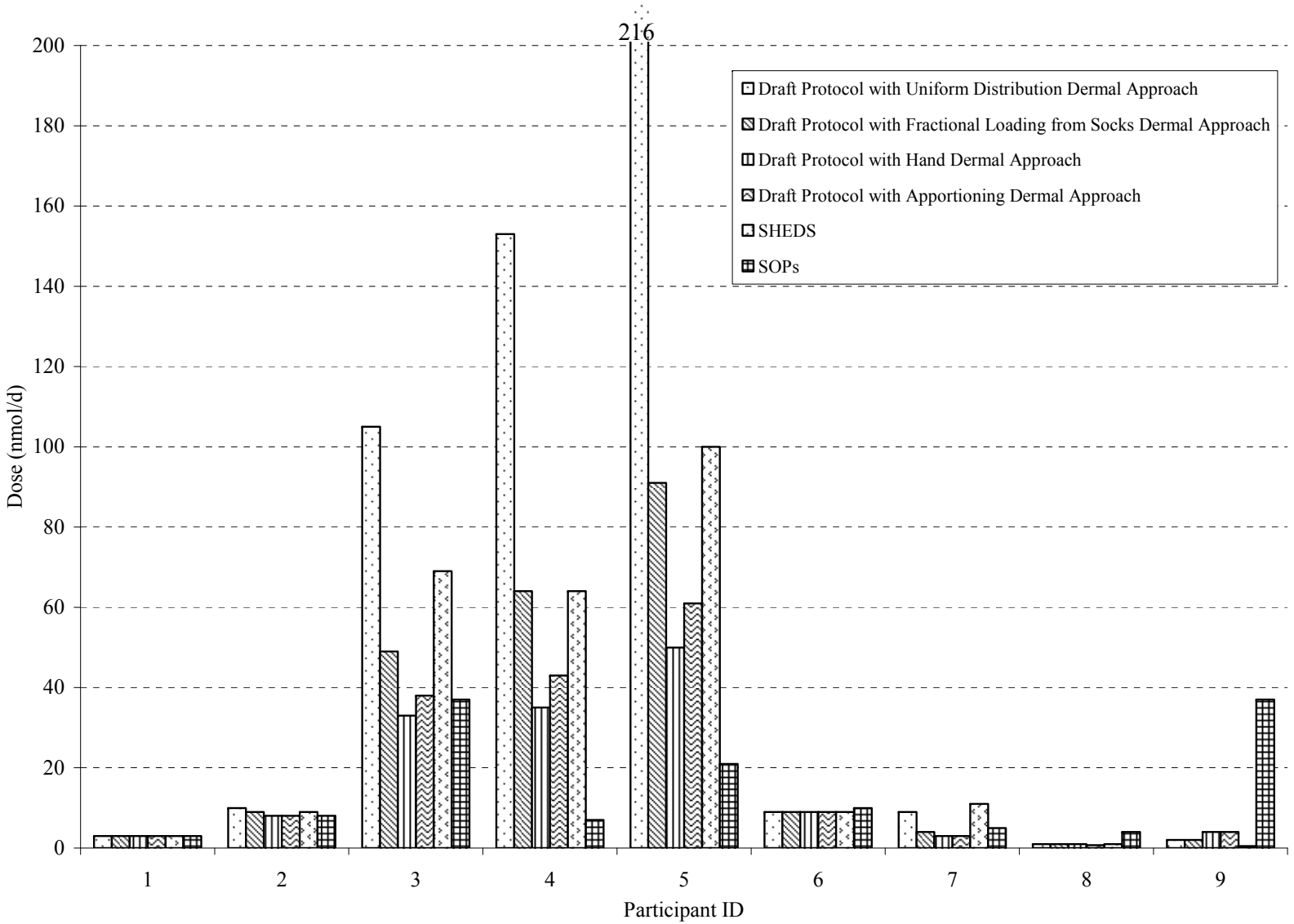
PID	Hand-to-Mouth (Indirect Ingestion) Exposure Estimate using *Draft Protocol* (nmol/d)	Hand-to-Mouth Exposure Estimate from SHEDS (nmol/d)	Hand-to-Mouth Exposure Estimate from SOP (nmol/d)	Dietary Ingestion Exposure Estimate using *Draft Protocol*[a] (nmol/d)
1	0.004	0.7	0.02	4.8
2	0.01	1.4	0.1	14.5
3	0	92	0	19.3
4	1.2	104	4.3	0
5	2.0	188	12.1	0.6
6	0.3	0.8	1.1	16.1
7	0.4	16	2.6	0.8
8	0.2	2	1.3	0.7
9	3.4	0.5	21.5	0.6

606 [a]SHEDS typically uses a complex algorithm based on population data to estimate dietary ingestion. OPP uses DEEM to calculate
607 dietary probabilistic assessments from exposures to pesticide residues in foods that people eat. For this comparison, the dietary
608 ingestion exposure estimates generated from the *Draft Protocol* were used since they more accurately reflect the individual diets in
609 terms of the actual foods consumed.

610 Figure 1. Absorbed dose estimates for the nine participants, by methodology and dermal approach (nmol/d).

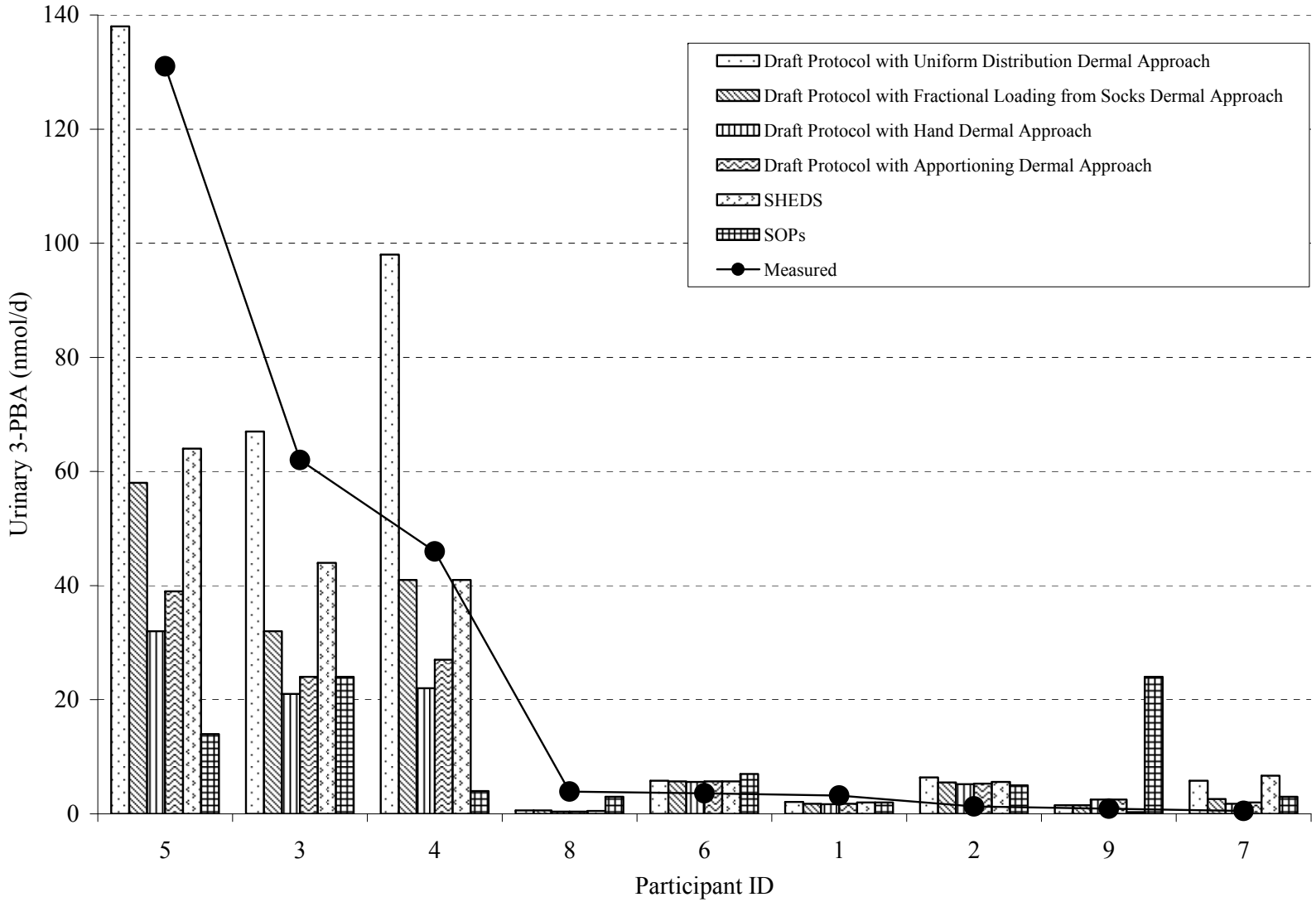
611 Figure 2. Comparison of the urinary 3-PBA estimates from the various methodologies with the measured values (nmol/d).

612 Figure 1.



613

614 Figure 2.



615

METHODOLOGIES FOR ESTIMATING CUMULATIVE HUMAN EXPOSURES TO CURRENT-USE PYRETHROID PESTICIDES

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SUPPLEMENTARY INFORMATION

MATERIALS AND METHODS

Pilot Observational Exposure Study

Socks were used to estimate the amount of pesticide residue that could be on the participating child's skin after normal play activities. Children wore the socks for one hour or longer while at home and engaged in normal play behavior, with the caregiver recording the time worn. A section (25 cm^2) of sock was then analyzed. One surface wipe sample was collected from the main play area of the house and one surface wipe sample was collected from a location inside the house where pesticide had been applied, as identified by the caregiver. Wipe samples were collected from a 929 cm^2 area on a hard surface and then analyzed. Indoor air samples were collected in the main play area of the house and outdoor air samples were collected from the front yard. Duplicate diet (all solid and liquid foods eaten) samples were also collected.

Each participating child provided a morning void urine sample. Each caregiver completed a 24-hr time activity diary for his/her participating child. The diary collected the time indoors, outdoors, and away from home; locations occupied; surfaces contacted; activities; activity level; and type of clothing worn. More information on the multimedia samples and the time activity diary can be found in Tulve *et al*. (2008).

A multi-residue analysis method was used to analyze the multimedia samples for 13 common synthetic pyrethroid pesticides (Tulve *et al.*, 2006). The multimedia measurements and activity pattern information were used as input parameters for the *Draft Protocol Aggregate Exposure Algorithms*, SHEDS-Multimedia, and residential SOPs. All pyrethroid pesticides measured in the collected samples that metabolize to 3-phenoxybenzoic acid (3-PBA) were considered for the cumulative exposure and dose estimates. Molar concentrations were used for all calculations.

RESULTS AND DISCUSSION

Pathway Contributions

Pathway contributions using the *Draft Protocol* with the fractional loading from socks dermal approach resulted in no change in the primary contributing route for each participant and only a slight change in the percent contribution. When the *Draft Protocol* using the hand dermal approach was considered, the primary contributing pathway became the dietary exposure route for Participant 8. Lastly, when the *Draft Protocol* using the apportioning dermal approach was evaluated, for each participant the primary contributing route of exposure was the same as the results for the hand dermal approach, except for Participant 9 where dermal became the predominant route of exposure contributing to the dose estimate.

For SHEDS: for Participants 1, 2, 6, and 9, the primary contributor to the dose estimate was the dietary route of exposure; the dermal route of exposure was the primary contributor to the dose estimate for Participants 3, 4, 5, and 7; and the indirect ingestion route of exposure was the primary contributor to the dose estimate for Participant 8. For the SOPs: for Participants 1, 2, and 6 the primary contributor to the dose estimate was the dietary route of exposure; for Participants 3, 4, 5, 7, 8, and 9 dermal was the primary contributor to the dose estimate.

Table S1. Child-specific inhalation rates (m^3/hr).

Inhalation Rates (m^3/hr)						
Participant	Age (yrs), Sex, Weight[a] (kg)	Sleeping/Napping	Indoor Quiet	Indoor Active	Outdoor Quiet	Outdoor Active
1	6, Male, 21	0.19	0.24	0.58	0.24	0.58
2	4, Male, 16	0.16	0.20	0.46	0.20	0.46
3	6, Male, 21	0.19	0.24	0.58	0.24	0.58
4	6, Female, 20	0.17	0.22	0.52	0.22	0.52
5	4, Female, 16	0.15	0.19	0.42	0.19	0.42
6	5, Male, 18	0.17	0.22	0.51	0.22	0.51
7	4, Female, 16	0.15	0.19	0.42	0.19	0.42
8	5, Female, 18	0.16	0.21	0.48	0.21	0.48
9	6, Male, 21	0.19	0.24	0.58	0.24	0.58

[a]Median weight values from CDC standard reference curves (Ogden *et al.*, 2002).

Figure S1. Bland-Altman plots showing the agreement between measured urinary 3-PBA concentrations and values estimated with the *Draft Protocol* using each of the four dermal approaches, SHEDS, and SOPs (nmol/d). Dashed lines represent *bias* (measured – estimated) and dotted lines represent *the 95% limits of agreement*.