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# Filling gaps between exposure modeling and the analysis of urinary biomarkers using personal air monitoring: An intervention study of permethrin used in home insecticide spray

Seon-Kyung Park[1] | Heon-Jun Lee[2] | Eugene Song[3] | Yerin Jung[1,4] | Hyun Jung Yoo[3] | Jeong-Eun Oh[2] | Hyeong-Moo Shin[5,6] | Jung-Hwan Kwon[1]

[1]Division of Environmental Science and Ecological Engineering, Korea University, Seoul, Republic of Korea

[2]Department of Environmental Engineering, Pusan National University, Busan, Republic of Korea

[3]Department of Consumer Science, Chungbuk National University, Chungbuk, Republic of Korea

[4]Department of Earth and Environmental Sciences, University of Texas at Arlington, Arlington, Texas, USA

[5]Department of Environmental Science, Baylor University, Waco, Texas, USA

[6]Department of Environmental and Occupational Health, University of California, Irvine, CA, USA

**Correspondence**
Jung-Hwan Kwon, Division of Environmental Science and Ecological Engineering, Korea University, 145 Anam-ro, Seongbuk-gu, Seoul 02841, Republic of Korea.
Email: junghwankwon@korea.ac.kr

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## Abstract

Permethrin is one of the most widely used active ingredients in spray-type home insecticides. However, indoor permethrin exposure resulting from the use of home insecticides is not well-characterized, as measured permethrin concentrations in indoor environmental and biological media with a known application rate are scarce. We conducted an intervention study with four participants for seven days. We conducted personal air monitoring and collected 24-h urine samples in which we quantified time-weighted average (TWA) permethrin concentrations in indoor air ($C_{air}$) and urinary concentrations of two permethrin metabolites, 3-phenoxybenzoic acid (3-PBA) and *cis*/*trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (*cis*/*trans*-DCCA). We also estimated (1) TWA $C_{air}$ using a simple indoor air model and (2) urinary excreted (UE) mass using a simple excretion model with both estimated and measured TWA $C_{air}$. Measurements of TWA $C_{air}$ from personal air monitoring were lower than those estimated from the indoor model by a factor of 2.9 to 49.4. The ratio of estimated to measured UE mass ranged 3.5–18.2 when using estimated TWA $C_{air}$ and 1.1–2.9 when using measured TWA $C_{air}$. Smaller ratios in estimating internal permethrin exposure from personal air monitoring suggest that personal air monitoring could reduce uncertainties in permethrin exposure assessment resulting from the use of spray-type insecticides.

**KEYWORDS**
air monitoring, exposure modeling, home insecticide, indoor air modeling, intervention study, permethrin

## 1 | INTRODUCTION

Pyrethroids have been widely used as insecticides worldwide since 1970s because of their low toxicity to mammals.[1] They have been used against malaria, dengue, Chikungunya and Zika viruses.[2,3] The global market value of pyrethroids has increased and is expected to grow in the future.[4,5] Epidemiologic evidence has shown that exposure to pyrethroids is associated with an increased risk of brain tumors, abnormal behaviors of children, neurological deficits, diabetes, and lung function, raising the

Seon-Kyung Park and Heon-Jun Lee contributed equally to this work.

need for characterizing exposure to pyrethroids.[6–10] A primary exposure pathway of pyrethroids is known to be food ingestion, but indoor exposure via home insecticide use is also an important pathway.[11,12]

Several methods have been applied to assess indoor exposure to pyrethroids, including indoor air monitoring, biomonitoring, and mathematical modeling for the indoor environment and a human body. For example, measured pyrethroid concentrations in indoor air samples were used to estimate external exposure to pyrethroids.[13–16] However, measured air concentrations were often significantly lower than those estimated from mathematical models.[15,16] Because pyrethroids have relatively high octanol–water partition constants and low vapor pressure,[17,18] they tend to deposit on floors and partition to dust particles[19,20] and other indoor surfaces such as furniture or wallpapers.[13,14] Thus, significant loss of pyrethroids via deposition and sorption after application could explain this observed difference.[15,16] Comparative studies of air monitoring and biomonitoring reported limited correlation between external and internal exposures.[21] Physiologically based pharmacokinetic (PBPK) models have also been used to estimate internal exposure to pyrethroids.[22–24] To the best of our knowledge, however, measured concentrations of pyrethroids in indoor and biological samples with a known application rate are scarce and no studies assessed indoor exposure to pyrethroids by evaluating an indoor air model with air monitoring and a PBPK model with biomonitoring.

The objectives of this present study are to estimate pyrethroid exposure from the use of spray-type home insecticides and to provide information or data gaps in assessing indoor pyrethroid exposure from mathematical modeling. In this study, focusing on permethrin as a model pyrethroid, we conducted a series of exposure assessment by evaluating measured and modeled concentrations of permethrin in indoor air and urine. To critically evaluate our indoor air model and excretion model, we conducted an intervention study by collecting personal air and urine samples during the entire intervention period. Note that this study was conducted to improve exposure assessment of biocides in compliance with the Republic of Korea's Biocide Risk Assessment System (BRAMS), a program developed for regulatory screening risk assessment of biocides.[25]

**Practical implications**

- Consumer exposure to permethrin due to the use of spray-type home insecticide could be an important exposure route.
- Clear intervention effects due to the use of home insecticide spray support the importance of consumer products.
- Personal air monitoring could be a relatively low-cost supplement to a screening model, especially for hydrophobic and strongly sorbing compounds, such as permethrin.

## 2 | MATERIALS AND METHODS

### 2.1 | Study participants and intervention study design

For the intervention study, we recruited four participants (P1–P4) who could stay home for most of their time. Participants were recruited following snowball sampling, giving preferences to those who participated (P2, P3, and P4) in our previous study in 2019,[12] and managed under the ethical approval of the Korea University Ethics Committee (KUIRB-2020-0082-02). The participants were healthy females aged 35–39 years.

From market research, permethrin is one of the most widely used active ingredients of spray-type home insecticides in Republic of Korea.[26] For this intervention study, we provided two types of products: (1) an intervention product (IP) that contains permethrin and (2) an alternative product (AP) that does not contain permethrin. The IP was also considered if the metabolites of other active ingredients were not 3-PBA and *cis/trans*-DCCA. The IP contains 0.26 g per 100 g of permethrin.

Each study volunteer participated for seven days in August 2020. In the first three days (period 1), participants were asked to use the AP to estimate background excretion of 3-PBA and *cis/trans*-DCCA. In the next two days (period 2), to observe the first intervention effect on permethrin exposure (i.e., increases in excretion of 3-PBA and *cis/trans*-DCCA), participants were asked to use the IP at least five times per day for at least 5 s, representing a typical heavy-use condition in Republic of Korea.[27] Three out of four participants used the IP without ventilation in the toilet, and P4 used the IP with high ventilation frequency (8 trials out of a total of 10 applications) in the balcony. In the last three days (period 3), participants were asked to use the AP, allowing us to observe the second intervention effect on permethrin exposure. During the entire intervention period, we asked our participants to change only the insecticide type (from AP to IP to AP) and to keep other lifestyle patterns routinely.

### 2.2 | Sample collection

Participants were asked to collect air samples around the breathing zone (details shown below) and urine samples and record all information relevant to samples in daily journals. Details of recoded information by participants are available in Table S1 and S2 (Supporting Information). Urine samples and sampling cartridges of mini-volume air samplers were stored in a Styrofoam container with dry ice until they were transported daily to the laboratory. Collected samples were stored at −20°C until permethrin and its metabolites were extracted.

Personal air monitoring was conducted using a mini-volume air sampler at a rate of 1.0 L $min^{-1}$ (Touch 220-5000TC, SKC Air Check,

Pittsburgh, PA, USA) with an XAD-2 cartridge (ORBO™ Supelpack™ 20u, 100/50 mg, SUPELCO, PA, USA) to measure the time-weighted average (TWA) concentration of permethrin in indoor air ($C_{air}$) inhaled by each participant.[28–30] To measure background air concentrations, an air pump was placed on the floor of the house where the participant spent the longest time during the day, and this sampling was conducted twice for 12-h. During period 2, the participant sampled the breathing zone air during each exposure event (10 times for each participant). They replaced the sampling cartridges immediately before the application of the IP, and air was pumped until they left the place of use.

## 2.3 | Chemical analysis

### 2.3.1 | Chemicals

3-PBA, *cis/trans*-DCCA, and *cis/trans*-permethrin were obtained from Cambridge Isotope Laboratories (>97.0% purity) (Andover, MA, USA). The solvents used were of high-performance liquid chromatography (HPLC) grade and were purchased from J.T. Baker (Phillipsburg, NJ, USA). Acetic acid was purchased from Wako (Osaka, Japan), and sodium acetate and β-glucuronidase/sulfatase type H-1 from *Helix pomatia* were purchased from Sigma-Aldrich (St. Louis, MO, USA).

### 2.3.2 | Indoor air

The analytical method of Dos Sanstos et al.[29] was used to quantify the *cis/trans*-permethrin concentrations in indoor air using the XAD-2 sorbent. XAD-2 resins were taken from the cartridge and transferred to 2.0 ml extraction solvent (*n*-hexane: ethyl acetate = 7:3, v/v). The solution was sonicated for 15 min. After collecting the extract, the remaining XAD-2 resins were extracted twice using the same procedure. The solvent extracts were combined in a 15 ml polyethylene tube and concentrated to dryness using a TurboVap II (Biotage, Uppsala, Sweden) at 40°C and reconstituted in 1 ml of *n*-hexane. The extracts were stored at −5°C until instrument analysis.

### 2.3.3 | Urine

The analytical method of Garí et al.[31] and Olsson et al.[32] with minor modifications, was used to quantify the concentrations of 3-PBA and *cis/trans*-DCCA in urine. Briefly, from each urine sample, 2.0 ml liquid was aliquoted and spiked with 10 ng of internal standards. β-Glucuronidase/sulfatase type H-1 from *H. pomatia* with a specific activity of approximately 500 units $mg^{-1}$ was used to hydrolyze possible glucuronide or sulfate conjugates. A buffer solution (6.0 ml) containing 33.3 mg of β-glucuronidase/sulfatase was used, giving a minimum of 990 units of activity per sample, which were then incubated for 17 h at 37°C. The SPE cartridge (OASIS HLB 60 mg, 3 $cm^3$; Waters Corporation, Milford, MA, USA) was preconditioned in succession with methanol:acetone (1:3, v/v) and HPLC-grade water containing 1% (v/v) acetic acid. The sample was then added and passed through a cartridge. To reduce interfering components, the cartridges were washed again with 1 ml of HPLC-grade water containing 1% (v/v) acetic acid. The cartridge was dried for 30 min, and the analytes were eluted using 3 ml of methanol:acetone (1:3, v/v). The extract was concentrated to dryness using nitrogen gas and reconstituted in methanol (0.5 ml). A more detailed description of the procedure has been reported in our previous study.[12]

### 2.3.4 | Instrumental analysis

3-PBA and *cis/trans*-DCCA in the extracts were analyzed by HPLC-tandem mass spectrometry (Agilent 1200 HPLC/6470 triple Quad; Agilent Technologies, Santa Clara, CA, USA). For separation of the analytes, a ZORBAX Eclipse XDB-C18 column (4.6 × 150 mm long, 3.5 μm; Agilent Technologies), fitted with a guard column of the same sorbent material (4.6 × 12.5 mm long, 5 μm; Agilent Technologies), was used. The mobile phase employed for the separation consisted of mobile phase A: a mixture of HPLC water with 5% methanol and 1% acetic acid, and mobile phase B: acetonitrile. The change in the gradient system was linearly scheduled as follows: 20% of phase B for 0–2 min, a linear increase to 50% of phase B for 3 min, a linear increase to 90% of phase B for 9–16 min, and a decrease to the original condition of 20% of phase A for 18–22 min. The total run time was 22 min.

The *cis/trans*-permethrin in the extracts was analyzed by gas chromatography–tandem mass spectrometry (Agilent 7890 B GC/7000C triple Quad; Agilent Technologies, Santa Clara, CA, USA) with an HP-5MS column (30 m × 250 μm id × 0.25 μm phase thickness) used for permethrin identification and quantification. The oven temperature started at 92°C for 2.5 min, increased by 15°C/min to 175°C (13 min hold time), and 20°C/min to 280°C (9 min). Helium was used as the carrier gas at a constant flow at 1.0 ml $min^{-1}$. The inlet, interface, and source temperatures were maintained at 250, 280, and 300°C, respectively, and a splitless mode was used for the injector. The mass spectrometer was operated in the electron impact ionization mode at 70 eV. Standards and samples were injected in the selected ion monitoring mode using three ions for *cis/trans*-permethrin (*m/z* 163.0, 165.0, 183.0).

### 2.3.5 | Quality assurance/quality control

For quality assurance and control, calibration curves, recoveries of internal standards, and method detection limits (MDLs) were determined. Ten calibration standards were used to construct a calibration curve ranging from 0.10 to 100 ng $ml^{-1}$ for urine samples and ranging from 1 to 2000 ng $ml^{-1}$ for biocidal products and air samples, and the linearity coefficient ($R^2$) was greater than 0.99. To check experimental and analytical precision, duplicate and replicate samples

were analyzed for every 10 samples, and the relative percentage difference was satisfied within 15%. Accuracy was determined by three replicate analyses and ranged from 102% to 120% in urine samples and from 107% to 108% in XAD-2 samples. The precision values were <15%. The MDLs, defined as the values corresponding to a signal-to-noise ratio of 3, were 0.46, 0.63, 0.09, 0.75, and 0.41 ng $ml^{-1}$ for *cis*- and *trans*-permethrin, 3-PBA, *cis*- and *trans*-DCCA, respectively. The recovery of permethrin metabolites and permethrin ranged from 59% to 118% for the urine samples and from 102% to 109% for the XAD-2 samples, respectively (Table S3, Supporting Information).

## 2.4 | Exposure models

The models in our previous study[12] were used to estimate permethrin concentration in indoor air and the mass excretion of 3-PBA and *cis/trans*-DCCA in urine. To estimate the TWA $C_{air}$ after the IP was used, we used a one-compartment indoor air model (used in BRAMS) that accounts for emission rates and removal rates via air change and decay. During the application of the product, the air concentration ($C_{air}$) is described by the following linear equation:

$$\frac{dC_{air}}{dt} = -(ACR + k_d)C_{air} + \frac{EMR}{V} \quad (1)$$

where *ACR* is the air change rate ($s^{-1}$), $k_d$ is the pseudofirst-order decay constant of permethrin ($s^{-1}$), *EMR* is the constant emission rate (μg $s^{-1}$), and *V* is the volume of the place where the product is used ($m^3$). After the application, $C_{air}$ is given:

$$\frac{dC_{air}}{dt} = -(ACR + k_d)C_{air} \quad (2)$$

The *EMR* was calculated by dividing the changes in product mass by the total daily spraying time. For the quantification of the used amount of the product, it was collected daily and weighed. For $k_d$, an estimated value (2.8 $h^{-1}$) using a spray-type product in a climate chamber,[15] was applied. Other model parameters (volume of room, room type, emission time) were taken from the participants' journals (Table S2).

Permethrin is eliminated from the body after conversion to 3-PBA and *cis/trans*-DCCA in the liver.[20,33] For each of the three study periods, the measured urinary excreted mass ($UE_{meas}$, μg) of 3-PBA and *cis/trans*-DCCA over time was calculated by multiplying the measured creatinine normalized concentration (μg $g_{creatinine}^{-1}$), time gap of urine excretion (s), body weight ($kg_{bw}$) and the average 24-h creatinine excretion (15.3 $mg_{creatinine}$ $kg_{bw}^{-1}$ $d^{-1}$).[34] To estimate time-dependent excreted mass ($UE_{estim}$) of 3-PBA and *cis/trans*-DCCA, we used a one-compartment urinary excretion model that accounts for only inhalation exposure, assuming that other exposure routes are minor during our study period.[35] We estimated inhalation exposure by using estimated $C_{air}$ from the indoor air model and measured $C_{air}$ from personal air monitoring.

The regression line of the cumulative sum of excreted masses over period 1 was considered as the background excretion of metabolites (Tables S4 and S5, Figure S1, Supporting Information). Parameters (inhalation rate, emission rate, air change rate, total liver clearance, blood volume, decay constant, and urinary excretion constant) for sensitivity analysis were performed using Monte Carlo simulation with 125 iterations. Distributions of input parameters are found at the truncation of the two standard deviation ranges.

## 2.5 | Data analysis

The intervention effect was assessed using the Wilcoxon signed rank test for individual participants ($p = 0.05$) under the null hypothesis of no intervention effects between the creatinine-normalized metabolite concentrations before (period 1) and after the intervention (periods 2 and 3) using R.[36] Sensitivity analysis was performed for three input parameters in the indoor air model, $k_d$, *ACR*, and *EMR*. Changes in $TWA_E$ were calculated within the variation of ±50% of those parameters.

# 3 | RESULTS

## 3.1 | Measured and estimated permethrin concentrations in indoor air

Permethrin was not detected in any background air samples (i.e., period 1). During period 2 when the IP was used, the measured TWA $C_{air}$ ($TWA_M$) of permethrin ranged from 0.0002 to 0.199 pg $m^3$ with the highest concentration in P4 (0.199 pg $m^3$) and the lowest in P4 (0.0002 pg $m^3$). Table S6 (Supporting Information) shows the full details of the sampling time, analyzed quantities of permethrin, and its TWA concentration for each participant.

For all participants, the estimated TWA $C_{air}$ ($TWA_E$) was greater than the $TWA_M$ (Table S5). The ratio of $TWA_E/TWA_M$ for P1, P2, P3, and P4 ranged 4.2–10.1, 2.9–9.6, 7.7–49.4, and 3.6–13.2, respectively. For each participant, the ratio tended to increase as the product usage increased and the one who applied the insecticide in a balcony with ventilation (P3) had the highest ratio. The volume of the place of use for P3 was larger than those for other three participants, causing more dilution.[37] Parameter sensitivities, percent changes in $TWA_E$ with respect to percent changes in *EMR*, $k_d$, and *ACR*, are shown in Figure S3. $TWA_E$ is more affected by *EMR* than $k_d$ and *ACR*.

## 3.2 | Measured urinary concentrations of two permethrin metabolites

Measured creatinine-normalized urinary concentrations of 3-PBA and *cis/trans*-DCCA during period 1 were lower than later periods (periods 2 and 3), showing intervention effects (Figure 1).

The background excretion of 3-PBA ranged from not detected (n.d.) (P3) to 1.85 ± 1.58 [μg $g_{creatinine}^{-1}$] (P1) and that of *cis/trans*-DCCA ranged from 0.19 ± 0.17 (P3) to 2.86 ± 1.83 [μg $g_{creatinine}^{-1}$] (P4). The regression line of the cumulative sum of 3-PBA and *cis/trans*-DCCA excretion was highly correlated over time ($r^2 > 0.88$) in period 1 (Table S5). In the case of P2, for *cis/trans*-DCCA, the correlation was low ($r^2 = 0.71$) because only three out of twelve samples were above the detection limit during period 1. All individual participants showed statistically significant intervention effects using the Wilcoxon signed sum test ($p = 0.05$) (Table S7, Supporting Information).

### 3.3 | Estimated urinary excretion of permethrin when using measured and estimated indoor air concentrations

For all participants, estimated cumulative excreted mass of 3-PBA and *cis/trans*-DCCA when using measured ($UE_{meas}$) indoor air permethrin concentrations was higher than when using estimated ($UE_{pred}$) indoor air permethrin concentrations (Figure 2). The ratio of $UE_{pred}$/$UE_{meas}$ obtained from personal air monitoring ranged 1.1–1.8 for *cis/trans*-DCCA and 1.7–2.9 for 3-PBA, whereas the ratio obtained from indoor air modeling ranged 3.5–11.1 for *cis/trans*-DCCA and 6.5–18.2 for 3-PBA (Table 1). This suggests that using measured permethrin concentrations from personal air monitoring can reduce overestimation of permethrin exposure.

## 4 | DISCUSSION

### 4.1 | TWA $C_{air}$ obtained by personal air monitoring and the indoor air model

In this study, we conducted low-tier exposure assessment to better characterize indoor permethrin exposure resulting from the use of spray-type home insecticides. Specifically, we collected a series of indoor air and urine samples from four participants who were asked to change the insecticide product from without permethrin to with permethrin to back to without permethrin. We then used the measured concentrations of permethrin in indoor air and of permethrin metabolites in urine to evaluate our indoor air model and excretion model. We observed that our indoor air model overestimated permethrin air concentrations by a factor of 2.9 to 13.2, depending on participants, even though it considered the decay constant. We also observed that applying estimated permethrin air concentrations as an input in our excretion model resulted in overestimation of excretion by a factor of 10 for 3-PBA and a factor 8 for *cis/trans*-DCCA. On the other hand, when applying measured permethrin air concentrations in the model, the excreted mass was overestimated by a factor of 2–4 for 3-PBA and a factor 1–2 for *cis/trans*-DCCA.

There are several reasons that the estimated TWA $C_{air}$ values were much greater than the measured values from personal air monitoring. First, it is likely that the removal of permethrin by the first-order decay constant and the air change rate was insufficient. The depositional removal rate constant (2.8 $h^{-1}$) measured by Clausen et al.[15] was obtained in a climate chamber. Although $TWA_E$ values were dependent more on *EMR* than $k_d$ and *ACR* at the same variation, parameter uncertainties in $k_d$ and *ACR* would be much greater than that of *EMR* because the use amount of the product was very precisely reported by the participants. Second, the geometric mean particle size of the spray used in Clausen et al.[15] was reported to be approximately 5 μm, 5–10 min after application. However, the measured particle size of the same IP spray used in the current study was predominantly smaller than 5 μm, 1 min after spraying.[26] Third, our study was conducted in participants' houses where other materials (e.g., wallpapers, floors, house dusts and furniture) could be also important. These materials may influence the deposition of permethrin aerosols as well as the sorption and partitioning of airborne permethrin.[38]

The relatively large deviation between $TWA_M$ and $TWA_E$ (Table S5) for P3 could be attributed to the application of the insecticide spray in a balcony that had a larger volume and ventilation rate than in a toilet. Although we did not restrict the place of home insecticide use, other participants used the product in a toilet. In general, a balcony has larger space and windows than a toilet in a typical Korean apartment. Although the model used in this study assumes that permethrin aerosol is immediately mixed in the space of use, aerosol particles may be deposited near the spraying point.[15] This suggests that the actual overall removal rate constant ($k_d$) is much greater than that proposed by Clausen et al.[15] or that there are other removal processes such as partitioning to other surfaces or being washed out by water and subsequently drained down-the-drain. Ventilation is an important factor affecting the indoor air change rate, even though it has a finite effect on the actual situation.[39,40] Because participants were asked to report only absence or presence of ventilation during their stay in the place of use, variable air change rates due to the angle of opening the window may have affected our model performance.[39] In addition, our model performance may have been affected by the lack of other important factors, such as the type of indoor materials, human movement patterns, and actual ventilation rates.

### 4.2 | Comparison of the intervention studies in 2019 (Park et al. 2021) and 2020

Participants P2, P3, and P4 also volunteered in our 2019 intervention study,[12] allowing us to compare urinary metabolite excretion patterns and indoor air modeling over two successive years. For P2, background creatinine-normalized concentrations of 3-PBA and *cis/trans*-DCCA were only slightly greater than those in 2019 by a factor of 1.18 and 1.35, respectively, implying that P2 was exposed to precursors of metabolites other than permethrin in home insecticide spray at similar levels. In contrast, P3 excreted lower levels of 3-PBA and *cis/trans*-DCCA in both the 2019 intervention

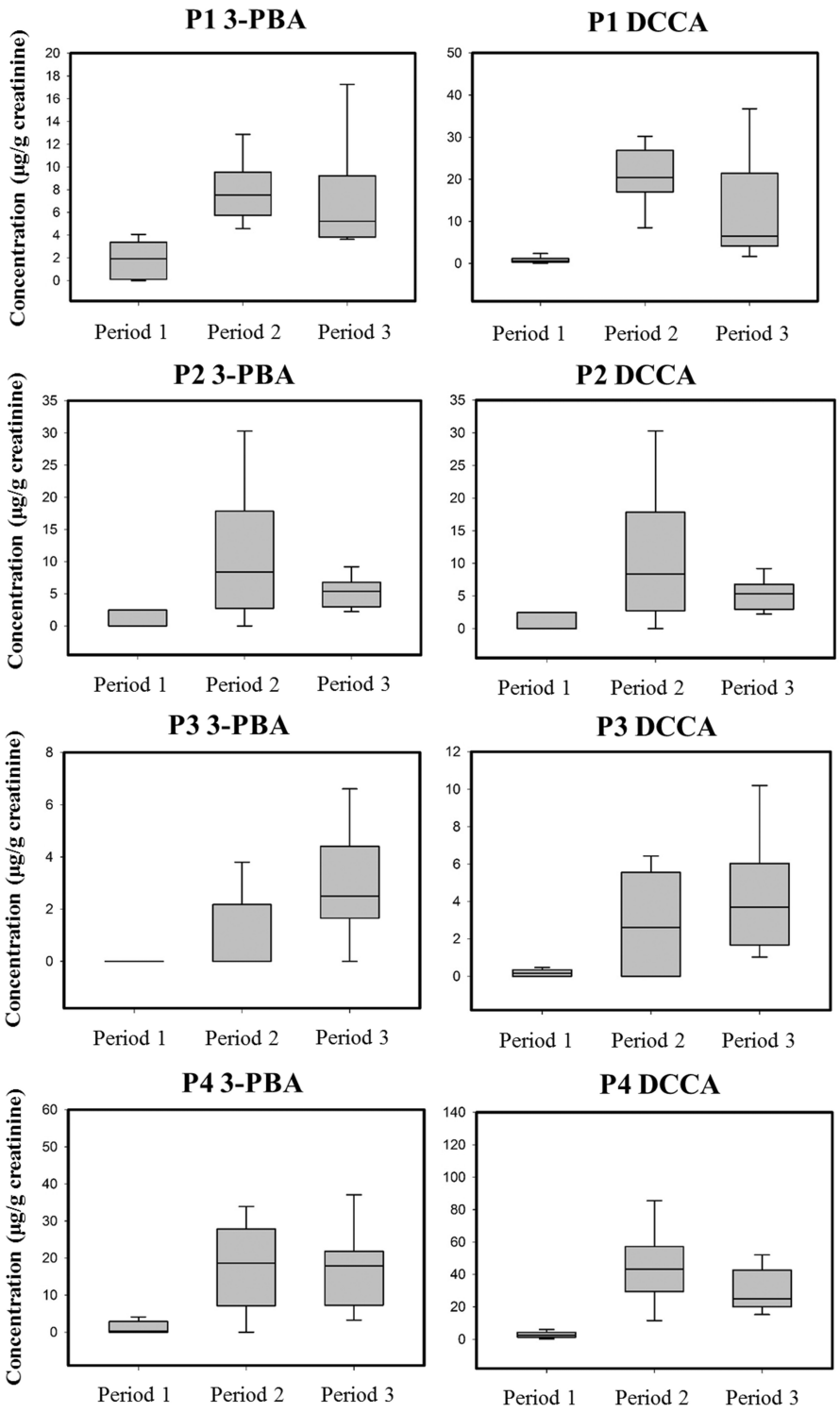


**FIGURE 1** Measured creatinine-normalized concentrations (µg/g creatinine) of 3-PBA and *cis/trans*-DCCA in 24-h urine samples ($U_{24h}$) of four study participants. Period 1 was the first 3 days of the study, during which participants were asked to use the alternative product (AP) as the only home biocide. Period 2 was during days 4 and 5 of the study, during which participants were asked to use only the intervention product (IP). Period 3 was the last 2 days of the study, during which participants were asked to use the AP as the only home biocide.

and this current study (Tables S4 and S8, Supporting Information). Studies on the excretion of *cis/trans*-DCCA and 3-PBA were usually within one year, and the correlation of the excretion level with seasons was poor.[41,42] Although only two participants volunteered in both the 2019 and 2020 studies, it is interesting to note that their background metabolite excreted masses were similar. It is likely that their personal behaviors affecting exposure to precursors of 3-PBA and *cis/trans*-DCCA (i.e., food consumption) did not change substantially. For P4, who participated in the 2019 study in the first morning void group, it was difficult to directly compare the excretion of 3-PBA and *cis/trans*-DCCA. The excretion of *cis/trans*-DCCA increased by 1.4-fold compared to that in 2019, but the excretion of 3-PBA decreased by 0.3-fold (Tables S4 and S8). Similarly, Attfield et al.[41] reported low reproducibility in the first and last void sampling.

All participants exhibited clear intervention effects in 2020, whereas no clear intervention effects were observed for P4 in the 2019 study (Table S7). In the 2019 intervention study, P4 belonged

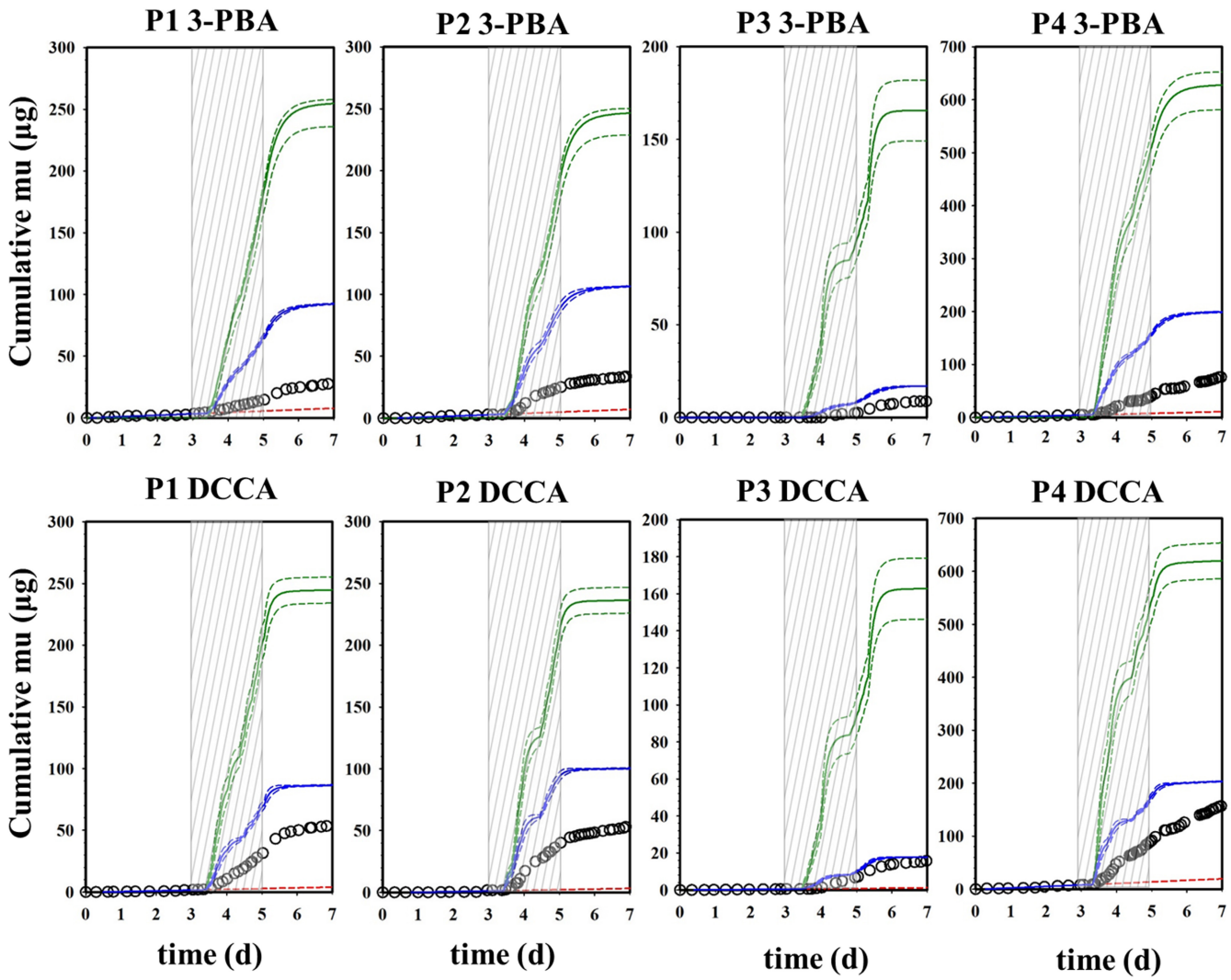


FIGURE 2 Cumulative mass ($m_u$) of 3-PBA and *cis*- and *trans*-DCCA in the urine during the intervention study (days 1–3 and 6–7 are background exposure, days 4–5 are intervention with IP) of participants P1–P4. Circles represent the measured molar masses of 3-PBA and *cis*- and *trans*-DCCA. Green lines represent the estimated cumulative amount of urinary excretion using the indoor air model. Blue lines represent the estimated cumulative amount of urinary excretion using personal air monitoring. Dashed lines indicate the 95% confidence limits (95% CI) obtained by a Monte Carlo simulation (125 iterations). Red dashed lines represent the background excretion based on the average excretion during period 1. The coarse areas indicate the intervention period.

to the first morning void group, and intervention effect was not significant for her, likely due to the short half-life of permethrin in the body. Another potential reason why we observed clear intervention effects on P4 in this study is that this participant mostly used the IP in more isolated places of the house without strong mechanical ventilation, although the total use amount of the IP was even smaller than those in the previous study.[12] In the case of P2, $UE_{meas}$ increased compared to that in 2019 (Tables 1, S9, S10, and Figure S2, Supporting Information), and since the exposure occurred in the same place, it is likely that the amount of used IP increased slightly or that the ventilation rate was decreased. The decrease in the ratio of $UE_{pred}/UE_{meas}$ in indoor air modeling was affected by the increase in $UE_{meas}$ (Tables 1 and S10). In addition, the $UE_{meas}$ of P3 increased compared to that in 2019 due to the smaller volume of the place of use, although the applied amount of IP was reduced (Table 1, S9, S10, and Figure S2, Supporting Information). The $UE_{pred}/UE_{meas}$ of indoor air modeling affected both $UE_{meas}$ and $UE_{pred}$ and was more affected by the increase in $UE_{meas}$.

### 4.3 | Filling the gap of modeling and metabolite excretion by air sampling

It was demonstrated that indoor air monitoring was successful in explaining the gap between internal and external exposure assessments. The strength of this study lies on that it was the most comprehensive exposure assessment study incorporating indoor air modeling, personal air monitoring, excretion modeling, and urinary biomarker analysis. At least for the case of permethrin used in home insecticide spray, personal air monitoring could be an important

**TABLE 1** The ratio of the predicted-to-measured excretion ($UE_{pred}/UE_{meas}$) of two permethrin metabolites based on measured and estimated indoor air permethrin concentration. Mean values and 95% confidence limits (95% CI) obtained using Monte Carlo simulation are shown

| | | $UE_{pred}/UE_{meas}$ | | | |
|---|---|---|---|---|---|
| | | Personal air monitoring | | Indoor air model | |
| ID | Metabolite | Mean | 95% CI | Mean | 95% CI |
| P1 | *cis/trans*-DCCA | 1.6 | 1.6–1.6 | 4.5 | 4.3–4.7 |
| | 3-PBA | 3.2 | 3.2–3.2 | 8.8 | 8.5–9.1 |
| P2 | *cis/trans*-DCCA | 1.8 | 1.8–1.8 | 4.3 | 4.1–4.5 |
| | 3-PBA | 2.9 | 2.9 | 6.8 | 6.5–7.1 |
| P3 | *cis/trans*-DCCA | 1.1 | 1.1–1.1 | 10 | 9.0–11.1 |
| | 3-PBA | 1.7 | 1.7–1.7 | 16.6 | 14.9–18.2 |
| P4 | *cis/trans*-DCCA | 1.2 | 1.2–1.2 | 3.7 | 3.5–3.9 |
| | 3-PBA | 2.4 | 2.3–2.4 | 7.4 | 7.0–7.8 |

low-cost tool for refining exposure assessment. Urinary biomarkers are usually regarded as superior to external exposure modeling routinely used for screening chemical exposure usually for registration purposes,[43,44] although the analysis of excreted metabolites is time consuming and costly and may be interfered by other sources. In all cases in this study, $UE_{pred}/UE_{meas}$ were much smaller when $UE_{pred}$ was estimated with measured air concentrations from personal air monitoring, indicating that overestimation of TWA $C_{air}$ is the most important cause of the gaps and the gap in exposure assessment using urinary biomarkers and mathematical modeling could be filled by the augmentation of personal air monitoring. This could be extended to other hydrophobic organic chemicals that are likely to sorb to indoor surfaces significantly.

There are some limitations of this study. First, this study considered only one exposure route for permethrin. Other compounds with different physicochemical properties behave differently in the residential environment, requiring considerations of other exposure routes such as dermal uptake via deposited aerosols.[45–47] Second, a simple one-compartment indoor air model employed should result in rather inevitable overestimation of indoor air concentrations and thus inhalation exposure to permethrin. Third, a small number of participants ($n = 4$) limits further generalization of exposure assessment although the intervention effects were observed at an individual level. People differ and vary in their living patterns (e.g., place of exposure, ventilation), and processes of absorption, desorption, metabolism, and excretion.

Although exposure prediction based on mathematical models is preferred for risk assessment at a screening stage to avoid underestimating risks, personal air monitoring could be a very reasonable refinement at the high-tier exposure assessment because it reflects specific environmental conditions of receptors. Many previous studies have reported the persistence of pyrethroids in indoor environments and their tendency to be deposited onto various indoor materials (furniture, dust, etc.).[14,20] Because it is often not feasible to account for variability in these processes,[48,49] including indoor air models, breathing zone air monitoring should be a good alternative to reflect complicated exposure conditions.

## 5 | CONCLUSIONS

In this seven-day intervention study with four participants, we characterized indoor permethrin exposure resulting from the use of insecticide spray at home by using various exposure assessment methods: indoor air modeling, personal air monitoring, excretion modeling, and biomonitoring. We observed that our indoor air model was too simple to represent the fate and transport of permethrin in the indoor environment after application, but personal air monitoring reduced uncertainties in exposure assessment against measured urinary excreted mass of permethrin metabolites. This suggests that personal air monitoring can account for site-specific exposure conditions such as ventilation, partitioning to indoor surfaces, and other removal processes. Although mathematical models are useful for assessing exposure to a large number of chemicals when measurements are not available, personal air monitoring would be an ideal method for assessing exposure to hydrophobic organic chemicals that are released to indoor air and whose primary exposure route is inhalation. Because this study considered only one study compound and one exposure route, future studies may need to consider a large number of biocides and all potential exposure routes to better characterize indoor exposure to biocides from the use of home insecticides.

### AUTHOR CONTRIBUTIONS

Seon-Kyung Park: conceptualization, data curation, software, methodology, investigation, and writing – original draft preparation. Heon-Jun Lee: data curation, methodology, investigation, and writing – original daft preparation. Eugene Song: data curation and investigation. Yerin Jung: data curation, and Investigation. Hyun Jung Yoo: supervision and funding acquisition. Jeong-Eun Oh: conceptualization and supervision. Hyeong-Moo Shin: methodology and writing – review & editing. Jung-Hwan Kwon: conceptualization, methodology, funding acquisition, supervision, and writing - review & editing.

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### CONFLICT OF INTERESTS

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

## ORCID

*Seon-Kyung Park* https://orcid.org/0000-0001-8252-2950
*Yerin Jung* https://orcid.org/0000-0003-2276-9585
*Jung-Hwan Kwon* https://orcid.org/0000-0002-6341-7562

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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