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# Exposure to permethrin used as a home insecticide: A case study comparing model predictions and excretion of metabolites

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ABSTRACT

Pyrethroids have been widely used as an active ingredient in home insecticide products since the 1960 s. Although their occurrence in indoor environments has been studied, the contribution of home insecticide application to the aggregate exposure to pyrethroids is not well known. The objective of this study was to estimate the consumer exposure to permethrin, a representative pyrethroid, via the use of home insecticide spray during the summer season using biomonitoring and personal exposure modeling. Exposure to permethrin was assessed by analyzing its urinary metabolites, 3-phenoxybenzoic acid (3-PBA) and *cis/trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropan carboxylic acid (*cis/trans*-DCCA), for a group of consumers ($n = 27$). The levels of metabolites were also compared with those predicted by a screening exposure model considering personal exposure parameters. The levels of metabolites in 15 participants increased significantly ($p < 0.05$) with the application of home insecticide products, thereby suggesting that the heavy use of home insecticides during summer could be an important exposure route of permethrin in addition to other sources, such as food consumption. The total amount of excreted 3-PBA and *cis/trans*-DCCA was lower than the amount estimated by the exposure model for most participants by a factor of 0.9–861.0. These differences could be attributed to the rapid loss of permethrin after application, including sorption to indoor surfaces, reaction with indoor substances, individual biological variations, and ventilation during application. However, the screening exposure model used for the initial safety assessment of biocidal products generally performed well because it did not underestimate the personal exposure to permethrin during the application of home insecticide spray.

## 1. Introduction

People spend most of their time indoors and are exposed to various chemical substances contained in consumer products, such as personal care products, insecticides, and preservatives (Hahn et al., 2005; Weschler, 2009). Among the many chemical substances to which people are exposed, active biocidal chemicals are of prime concern because of their intrinsic toxicity. Insecticides are widely used in large quantities to control pests, and pyrethroids are one of the major active ingredients of home insecticide products. Owing to their relatively low toxicity to mammals and ready biodegradability ( Narendra et al., 2008; Palmquist et al., 2012), they are believed to be safer than earlier insecticides (Palmquist et al., 2012). Pyrethroids are widely used for many purposes, including agriculture, building protection, and gardening (Atwood and Paisely-Jones, 2017; Song et al., 2014; Tang et al., 2018).

For aggregate exposure assessment, it is necessary to determine the uptake of pyrethroids from many available routes of exposure. Studies have been conducted on the general population to evaluate the level of overall exposure to pyrethroids and have shown that the levels of excreted metabolites vary significantly between individuals and countries (Barr et al., 2010; Heudorf and Angerer, 2001; Li and Kannan, 2018; Naeher et al., 2010). This large individual variation in exposure to

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pyrethroids can be attributed to the consumption of contaminated foods (Quindroit et al., 2019; Schettgen et al., 2002), occupational exposure (Kimata et al., 2009; Kolmodin-Hedman et al., 1982; Song et al., 2014), and the use of pyrethroids in gardening and home insecticides (Heudorf et al., 2006). Although food consumption is regarded as the main route of pyrethroid exposure in the general population (Quindroit et al., 2019; Schettgen et al., 2002), the use of home insecticides can be an important route of exposure (Sawar, 2015), especially when they are heavily used to control pests during summer. For example, Berger-Preiß et al. (2009) performed biomonitoring of metabolites over24 h in a model room using an insecticide spray. The analysis of urinary metabolites 24 h after exposure to the product revealed that the use of home insecticides significantly increased the level of their excretion compared with the level of background excretion. Because the half-life of pyrethroids in the body is only 6–13 h (Eadsforth and Baldwin, 1983; Leng et al., 1997a, 2006; Ratelle et al., 2015; Wollen et al., 1992), exposure to pyrethroids was assessed by measuring the level of their urinary metabolites (Garí et al., 2018; Olsson et al., 2003), even though some fractions were still in their original form (Godin et al., 2010). Common metabolites were found from different pyrethroids. For example, 3-phenoxybenzoic acid (3-PBA) forms from cyphenothrin, cypermethrin, deltamethrin, and permethrin, among others; *cis/trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropan carboxylic acid (*cis/trans*-DCCA) forms from cyfluthrin, cypermethrin, transfluthrin, and permethrin; and *trans*-chrysanthemumdicarboxylic acid forms from allethrin, prallethrin, and imiprothrin, among others. Common stable metabolites from various parent compounds make it difficult to quantitatively assess the exposure to specific compounds.

In this study, we performed biomonitoring with personal exposure modeling for consumers who use home insecticide sprays during the summer season in Korea. Permethrin was chosen as a model pyrethroid because of its high market share. Twenty-four-hour ($U_{24h}$) and first morning void ($U_F$) samples were collected from 8 and 19 participants, respectively, for 7 d while they used a home insecticide containing permethrin. An indoor air model describing the inhalation exposure to permethrin was used. Furthermore, a one-compartment excretion model was used to predict the excretion of metabolites, and the prediction was compared with the amount of metabolites, 3-PBA and *cis/trans*-DCCA. To the best of our knowledge, this is the first study to compare the chemical analysis of urinary metabolites and their estimated excretion using a one-compartment excretion model and the ambient concentration predicted by an indoor air model for heavy use of home insecticide products containing permethrin.

## 2. Material and methods

### 2.1. Chemicals and materials

The two native standards of 3-PBA and *cis/trans*-DCCA (1:1) and their internal standards ($^{13}C_6$-3-PBA and *trans*-DCCA-$d_3$, respectively) were purchased from Cambridge Isotope Laboratories (>97.0% purity) (Andover, MA, USA). Acetone, acetonitrile, high-performance liquid chromatography (HPLC)-grade water, and methanol were purchased from J.T. Baker (Phillipsburg, NJ, USA). Acetic acid was obtained from Wako (Osaka, Japan), and sodium acetate and β-glucuronidase/sulfatase type H-1 from *Helix pomatia* were obtained from Sigma-Aldrich (St. Louis, MO, USA).

Permethrin is one of the most widely used active ingredients in spray-type pest control products in Korea. Because 3-PBA and *cis/trans*-DCCA, which are major urinary metabolites of permethrin, can also be produced from other pyrethroids (Eadsforth and Baldwin, 1983; Leng et al., 1997a, 1997b), the intervention product (IP) and the alternative product (AP) were selected with care. IP was preferred among products containing a high concentration of permethrin according to a market survey. AP was chosen among products with significantly fewer active ingredients that produce 3-PBA and *cis/trans*-DCCA. In addition, participants were asked not to use the AP as frequently as the IP. The concentration of permethrin in the IP was 0.260 g per 100.0 g whereas that of AP was 0.072 g per 100.0 g.

### 2.2. Consumer panel

For the intervention study, 27 housewives were recruited in Korea, following the approval of the study by the Chungbuk National University Ethics Committee (CBNU-201906-BM-857–01). All participants were healthy female volunteers (33–47 years old) who spent most of their time at home. For eight participants in Busan, $U_{24h}$ samples were collected for 7 d, whereas only $U_F$ samples of the day were collected from 19 other participants (four from Chungju, nine from Gyeongsan, one from Busan, and five from Gimhae). A Styrofoam box containing dry ice was supplied to all participants, and they were asked to collect their urine in a polypropylene sampling bottle and store it in the box, which was collected and transported daily to the laboratory.

All usage patterns of the IP and AP were recorded in daily journals by the participants. They were asked to record exposure information, such as time, place, frequency of use, and ventilation. The format of the daily journals for volunteers is shown in Table S1. Other personal information required for exposure modeling (i.e., age, body weight (BW), and home floor plan) was also obtained.

### 2.3. Exposure scenario

The intervention study was conducted for 7 d per participant during the summer season (August to September). Period 1 was the first 3 d without exposure to IP. Period 2 was during days 4 and 5 of the study, during which participants were asked to use only the IP at least five times per day with a spraying time>5 s, representing a normal heavy-use condition. Period 3 was the last 2 d of the study. During periods 1 and 3, participants were asked to use the AP as the only home biocide. The levels of excreted 3-PBA and *cis/trans*-DCCA in urine samples during period 1 were defined as the personal background excretion of participants because 3-PBA and *cis/trans*-DCCA could be produced from various pyrethroids and other chemicals such as those in foods (Hermant et al., 2018; Quindroit et al., 2019; Schettgen et al., 2002).

### 2.4. Biocidal product analysis

For the analysis of pyrethroid insecticides in biocidal products, 0.10 g of the liquid from the sample was diluted with methanol and 100 ng of the labeled internal standard (permethrin-$d_5$, cypermethrin-$d_5$, cyhalothrin-$d_5$, and deltamethrin-$d_5$). The solution mixture was extracted by sonication for 30 min at 40 °C. The extract was then filtered with a polytetrafluoroethylene syringe filter (0.45 μm), concentrated under a gentle stream of nitrogen, and reconstituted with 1 mL of methanol. The samples were analyzed using an Agilent 1200 HPLC system equipped with a 6470-electrospray triple-quadrupole mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) with a ZORBAX Eclipse XDB-C18 column (4.6 × 150.0 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).

### 2.5. Urine extraction procedure and creatinine measurement

The analytical method used by Garí et al. (2018) and Olsson et al. (2003), with minor modifications, was used to determine pyrethroid metabolite concentrations in urine. Each 2 mL urine sample was transferred into a polypropylene tube for analysis, and 10 ng of $^{13}C_6$-3-PBA and *trans*-DCCA-$d_3$ was added as an internal standard. To hydrolyze possible glucuronide or sulfate conjugates, β-glucuronidase/sulfatase type H-1 from *H. pomatia* was used (specific activity of approximately 500 units·mg$^{-1}$). An amount of enzyme providing 990 units of activity dissolved in 6.0 mL of 0.2 M acetate buffer (3.1 mL of acetic acid and 9.7

**Table 1**
Parameters used in the indoor air model and the physiologically based pharmacokinetic model.

| Parameter | | Value | Unit | Reference |
|---|---|---|---|---|
| Air change rate[a] | Living room | 0.5 | $h^{-1}$ | NIER, 2014 |
| | Kitchen | 2.5 | $h^{-1}$ | |
| | Bed room | 1.0 | $h^{-1}$ | |
| | Toilet | 2.0 | $h^{-1}$ | |
| | Unspecific | 0.6 | $h^{-1}$ | |
| | Window open | 2.0 | $h^{-1}$ | Wallace et al. 2002 |
| Volume of room[b] | House floor plan | | $m^3$ | Daily journal |
| | Living room | 33.3 | $m^3$ | NIER, 2014 |
| | Kitchen | 24.5 | $m^3$ | |
| | Bedroom | 30.3 | $m^3$ | |
| | Toilet | 9.3 | $m^3$ | |
| | Unspecific | 8.0 | $m^3$ | Bremmer et al. 2006 |
| Usage start time | | | | Daily journal |
| Application | Use frequency × Spray time | | s | Daily journal |
| Exposure duration | | | s | Daily journal |
| Rate of product emission | | 1.2 | $g{\cdot}s^{-1}$ | Measured |
| Product concentration | (IP) permethrin | 0.26 | $g{\cdot}100\ g^{-1}$ | Measured |
| | (AP) permethrin | 0.072 | $g{\cdot}100\ g^{-1}$ | |
| Absorption fraction | Absorption via the inhalation route was set to 100% | 0.7 | | Egeghy et al. 2011 |
| Inhalation rate | Average inhalation rate of woman(light-intensity activity) | 0.007 | $m^3{\cdot}h^{-1}{\cdot}kg^{-1}$ | NIER 2019 |
| First order decay constant | | 2.8 | $h^{-1}$ | Clausen et al. 2020 |
| Urinary excretion rate | *cis*-DCCA | 0.000036 | $s^{-1}$ | Ratelle et al. 2015 |
| | *trans*-DCCA | 0.000043 | | |
| | 3-PBA | 0.000034 | $s^{-1}$ | |

[a] The representative value of the air change rate in each house space was obtained from the NIER (2014); 2 $h^{-1}$ was applied for participants who reported ventilation.
[b] The house floor plan was used to estimate the volume. In cases where there was no house floor plan, default room volumes from the NIER (2014) and Bremmer et al. (2006) were used.

g of sodium acetate in 1 L of water) was added. The samples were incubated for 17 h at 37 °C and then extracted using solid-phase extraction. OASIS HLB cartridges (60 mg, 3 $cm^3$; Waters Corporation, Milford, MA, USA) were preconditioned in succession with 1 mL of methanol:acetone (1:3, v/v) and 1 mL of HPLC-grade water containing 1% (v/v) acetic acid. The sample was loaded through the cartridge, and the cartridges were washed again with 1 mL of HPLC-grade water containing 1% (v/v) acetic acid and dried for 30 min. After drying, the cartridges were eluted with 3 mL of methanol:acetone (1:3, v/v). The extract was concentrated to dryness using a TurboVap II (Caliper Life Sciences, Hopkinton, MA, USA) and reconstituted in 0.5 mL of methanol. For the measurement of the creatinine concentration, urine samples were sent to an analytical laboratory (Seegene Medical Foundation, Seoul, Republic of Korea).

### 2.6. Exposure and excretion model

#### 2.6.1. Prediction of ambient $C_{air}$

The changes in air concentration ($C_{air}$) of permethrin with time $t$ during product spraying are given as follows:

$$\frac{dC_{air}}{dt} = -(\lambda + k_d)C_{air} + \frac{E}{V} \quad [1]$$

where $\lambda$ is the air change rate ($s^{-1}$), $k_d$ is the first-order decay constant of permethrin ($s^{-1}$), $E$ is the constant emission rate ($\mu g{\cdot}s^{-1}$), and $V$ is the volume of the area ($m^3$) where the insecticide was used. The indoor air concentration was estimated with an experimentally determined $k_d$ value of permethrin (2.8 h) using a climate chamber by Clausen et al. (2020) or without considering $k_d$. After product use, $C_{air}$ decays exponentially as follows:

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

After participants left the area of application, we assumed that their exposure to permethrin was negligible because of mixing, ventilation, deposition, sorption, and other removal processes. The model parameters were estimated individually based on the information in the participants' daily journals (Table S2). The emission rate was estimated by multiplying the use frequency, spraying time, and product concentration. The volume of the area of use was calculated based on the floor plan of the participants' houses. When the house floor plan was not available, default values from the National Institute of Environmental Research of Korea (NIER, 2014) were used (Table 1). The air change rate was set at 2 $h^{-1}$ when participants had ventilation (Wallace et al. 2002). We also compared the model outputs with and without considering $k_d$.

#### 2.6.2. One-compartment excretion model

To model the behavior of permethrin and its metabolites in the body, a one-compartment model was used. The model assumed that the major route of exposure was inhalation when spray-type insecticides were used. The exposure of dermal permethrin uptake when using a spray is known to be <1% (Tomalik-Scharte et al., 2005). The mass of permethrin in the body ($M_P$) when using the product can be expressed as follows:

$$\frac{dM_P}{dt} = f_{abs}C_{air}Q_{inh} - CL{\cdot}M_P/BV \quad [3]$$

where $f_{abs}$ is the absorption fraction assumed to be unity, $Q_{inh}$ is the inhalation volume flow rate based on the participant's BW ($m^3{\cdot}s^{-1}$), $CL$ is the total liver clearance for permethrin ($m^3\ s^{-1}$), and BV ($m^3$) is the blood volume (Table 1). After using the product, the amount of permethrin in the body ($M_p$) is given as follows:

$$\frac{dM_P}{dt} = -CL{\cdot}M_P/BV \quad [4]$$

Because permethrin is metabolized rapidly in the body and is too hydrophobic to be excreted through urine, we hypothesized that all of the absorbed permethrin was eliminated in the form of three metabolites, namely 3-PBA and *cis/trans*-DCCA. The rate of urinary excretion of each metabolite ($\frac{dM_{u,i}}{dt}$) was estimated as follows:

$$\frac{dM_{u,i}}{dt} = k_{eu,i}M_p\frac{MW_i}{MW_p} \quad [5]$$

where $M_{u,i}$ is the mass of metabolites excreted (μg), $k_{eu,i}$ is the first-order urinary excretion rate constant of each metabolite based on the absorbed

**Table 2**
Parameters for the Monte-Carlo analysis.

| Parameter | Distribution | CV | Reference |
|---|---|---|---|
| Inhalation rate ($Q_{inh}$) | N | 0.003 | NIER, 2019 |
| Emission rate | N | 0.1 | measured |
| Air change rate | N | 0.2 | NIER, 2014 |
| CL | L | 0.5 | Mallick et al. 2020 |
| Blood Volume | L | 0.22 | Mallick et al. 2020 |
| Decay constant ($k_d$) | N | 0.1 | Clausen et al. 2020 |
| Urine excretion constant *cis*-DCCA | N | 0.4 | Ratelle et al. 2015 |
| Urine excretion constant *trans*-DCCA | N | 0.2 | Ratelle et al. 2015 |
| Urine excretion constant 3-PBA | N | 0.1 | Ratelle et al. 2015 |

(N, normal; L, log-normal).

mass of permethrin ($s^{-1}$), and $MW_i$ and $MW_p$ are the molar masses of each metabolite and permethrin, respectively. Blood volume was calculated from an equation for women based on age (Ciffroy et al., 2017) and all other parameters were taken from Mallick et al. (2020). The inhalation rate was used assuming light-intensity activity of females and was adjusted for the participants' BWs (NIER, 2019). Inhalation absorption was assumed to be 70% (Egeghy et al. 2011). The values of the first order urinary excretion rate constant of metabolite were estimated to be 0.000043, 0.000036 $s^{-1}$ and 0.000034 $s^{-1}$ for *cis*-DCCA, *trans*-DCCA and 3-PBA, respectively, according to the method used by Ratelle et al. (2015), in which whole urine samples were analyzed up to 72 h after volunteers ingested permethrin (*trans/cis* = 60:40) equivalent to 0.1 $mg{\cdot}kg_{bw}^{-1}$. To compare the urine excretion metabolite and excretion model, 15.3 creatinine $mg{\cdot}kg^{-1}$ $d^{-1}$ was used to convert creatinine normalized concentration to mass.

### 2.6.3. Monte-Carlo analysis

Monte-Carlo simulations were performed for 125 iterations (Ritter et al. 2011). The assumed distributions and coefficients of variation (CV) of the model parameters are listed in Table 2. To avoid extreme outliers, the distribution was truncated symmetrically in the range of two standard deviations from the mean.

### 2.7. Intervention effect and modeled vs. Measured metabolite excretion

The intervention effect was evaluated by comparing the creatinine-normalized metabolite concentrations in urine before (period 1) and after the use of the IP (periods 2 and 3) using the *t*-test with a null hypothesis of no intervention effects. A one-tailed test was conducted to determine the statistical significance. Background excretion of *cis/trans*-DCCA and 3-PBA was estimated for the first 3 d. The sum of the regression lines in the background with the amount of excretion predicted by the model was compared with the experimental metabolite excretion.

### 2.8. Instrumental analysis

For the analysis of permethrin in the products and 3-PBA and *cis/trans*-DCCA in the urine samples, an Agilent 1200 HPLC system equipped with a 6470-electrospray triple-quadrupole mass spectrometer (Agilent Technologies, Santa Clara, CA, USA) was used for the separation and quantification of target compounds in the final extracts in negative mode. Analytes were separated on a ZORBAX Eclipse XDB-C18 column (4.6 × 150.0 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).

### 2.9. Quality assurance/quality control

The analytes were quantified using an internal standard method. A 10-point calibration ranging from 0.1 $ng{\cdot}mL^{-1}$ to 100.0 $ng{\cdot}mL^{-1}$ was performed for urine samples, which ranged from 1.0 $ng{\cdot}mL^{-1}$ to 2000.0 $ng{\cdot}mL^{-1}$ for biocidal products and air samples. The correlation coefficients ($r^2$) of the linear calibration curves were all > 0.99. To determine the experimental and analytical precision, duplicate and replicate samples were analyzed for every 10 samples, and the relative percentage difference was within 15%. The accuracy was determined by triplicate analyses, in which native and internal standards were spiked in the same manner as sample treatments and ranged from 102% to 120% in urine samples. The method detection limit (MDL) of pyrethroid metabolites was defined as the values corresponding to a signal-to-noise

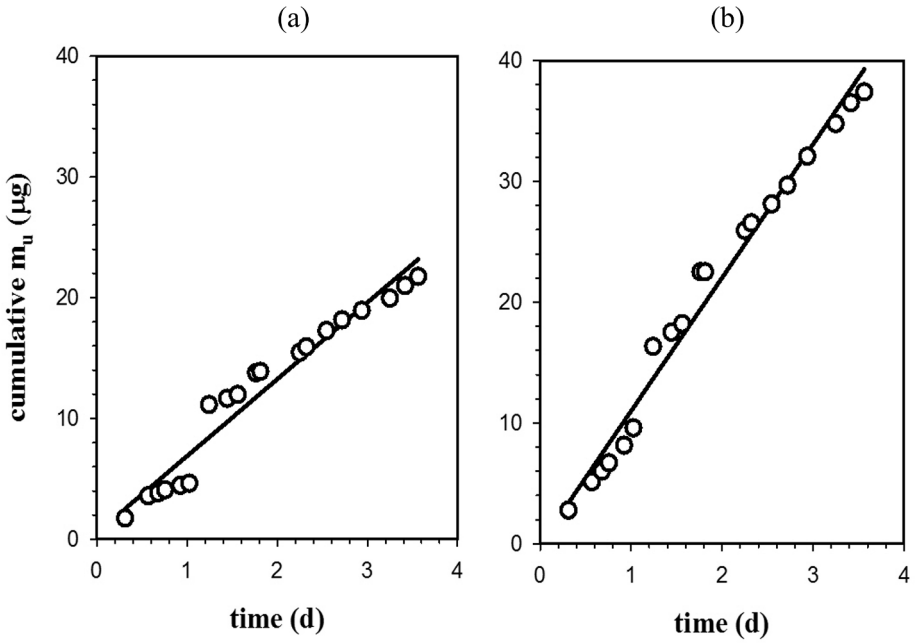


**Fig. 1.** Estimation of baseline excretion of (a) *cis/trans*-DCCA, and (b) 3-PBA by participant A5 as an example during period 1. The circles present the cumulative measured mass of urinary metabolites and the dashed lines show the linear regression during the period. The slopes of the regression were used as the individual baseline excretion of metabolites.

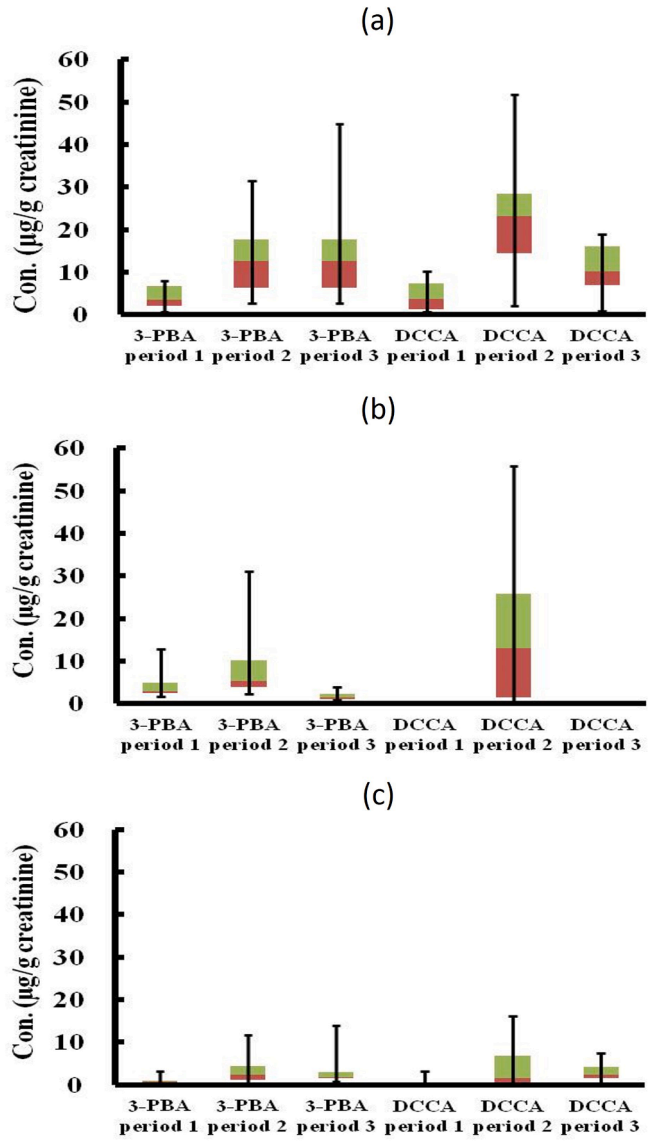


**Fig. 2.** Box-and-whisker plots showing the 3-PBA and *cis/trans*-DCCA concentration (μg/g creatinine) of 24-h samples (AU) participants A1 (a), A2 (b), A6 (c). Period 1 was the first 3 d of the study, during which participants were asked to use the alternative product (AP) as the only home biocide. 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 d of the study, during which participants were asked to use the AP as the only home biocide. Lines represent 25, 50, and 75 percentile values and the whiskers represent the maximum and minimum values.

ratio of 3. The MDLs were 0.09 ng·mL$^{-1}$ for 3-PBA, 0.75 ng·mL$^{-1}$ for *cis*-DCCA, and 0.41 for *trans*-DCCA. The recovery of pyrethroid metabolites ranged from 59% to 118% for the $U_{24h}$ samples (Table S3).

## 3. Results

### 3.1. Analysis of urine samples

Tables S4 and S5 summarize the average creatinine-normalized concentrations of 3-PBA and *cis/trans*-DCCA in urine samples during periods 1, 2, and 3 for all participants with box-and-whisker plots for $U_{24h}$ panels in Fig. 2 (participants A1, A2, and A6) and S1 (all participants in panel A). The ranges of the background excretion levels (period 1) of 3-PBA and *cis/trans*-DCCA in $U_{24h}$ panel were 0.45 ± 0.59–6.96 ± 14.05 (median = 4.1) μg·g$^{-1}_{creatinine}$ and 0.00 ± 0.00–10.41 ± 6.75 (median = 2.6) μg·g$^{-1}_{creatinine}$, respectively. The ranges of the background excretion levels (period 1) of 3-PBA and *cis/trans*-DCCA in $U_F$ panel were 1.37 ± 0.75–7.52 ± 1.56 (median = 3.6) μg·g$^{-1}_{creatinine}$ and 0.69 ± 0.73–10.65 ± 3.58 (median = 2.2) μg·g$^{-1}_{creatinine}$, respectively. As presented in Tables S4 and S5, the background urinary concentrations of 3-PBA were greater than those of *cis/trans*-DCCA for most of the participants. The background creatinine-normalized concentrations of 3-PBA and *cis/trans*-DCCA during period 1 were similar to those reported in the literature. The mean values of the creatinine-normalized concentration range of 3-PBA and *cis/trans*-DCCA were 0.10–6.50 μg·g$^{-1}_{creatinine}$ and 0.10–4.21 μg·g$^{-1}_{creatinine}$, respectively (Table S6).

To estimate the average excretion rate of 3-PBA and *cis/trans*-DCCA in an individual participant, a linear regression of $M_{u,i}$ vs. time was performed during period 1. The slope ranges for 3-PBA and *cis/trans*-DCCA were 0.40–6.36 μg·d$^{-1}$ and 0.00–11.05 μg·d$^{-1}$ for $U_{24h}$ samples and 1.35–17.17 μg·d$^{-1}$ and 0.68–31.53 μg·d$^{-1}$ for $U_F$ samples (Tables S7 and S8). Fig. 1 shows the background excretion of 3-PBA and *cis/trans*-DCCA in participant A5 during period 1.

To observe the intervention effects of a home insecticide spray, the excretion levels of 3-PBA and *cis/trans*-DCCA were compared during periods 1, 2, and 3. Significant differences ($p < 0.05$) in the mean excreted concentrations were observed in four (3-PBA) and six (*cis/trans*-DCCA) participants of the eight participants in the $U_{24h}$ group, whereas significant differences were observed in six (3-PBA) and five (*cis/trans*-DCCA) participants out of the 19 in the $U_F$ group (Tables S9 and S10).

### 3.2. Comparison of metabolite excretion with model estimation

Fig. 3 shows representative examples of the comparison of model predictions and measured cumulative excretion for participants (*cis/trans*-DCCA and 3-PBA): A1 (a and b), A2 (c and d), and A6 (e and f). Green lines represent estimated excretions without considering $k_d$ and blue lines considering $k_d$. Dashed lines represent the 95% upper and lower confidence limits (UCLs and LCLs) using the Monte-Carlo simulation. Red dashed lines present the background excretion based on the average excretion during period 1. Fig. S2 shows the results for other participants (A3-5 and 7-9). The levels of *cis/trans*-DCCA were below the detection limit for A2 (Fig. 3c) and A4 (Fig. S2c), thereby implying negligible background sources of *cis/trans*-DCCA. Although clear or slight intervention effects were observed for participants A1 and A2 (Fig. 2a–d), no intervention effects were observed for panel A6 (Fig. 2e and f). For all cases, the predicted cumulative excretion of metabolites was much higher than that analyzed from the urine samples, except for A1 (*cis/trans*-DCCA).

The difference between the cumulative excretion of metabolites (circles or dashed lines in Fig. 3 and S2) and the projected cumulative excretion using the baseline excretion during period 1 (red dashed lines in Fig. 3 and S2) shows the excess incremental exposure (IE) to permethrin when using the IP. For the $U_{24h}$ group, the ratios of predictions to measurements ($UE_{pred}/UE_{meas}$) at the end of the study without considering 1.0–31.3 and 1.3–37.4 for the 95% lower confidence limit (LCL) and 1.2–40.6 and 1.6–48.5 for the 95% for upper confidence limit (UCL) for *cis/trans*-DCCA and 3-PBA; they were 0.9–24.7 and 1.1–30.3 for the LCL and 1.1–31.8 and 1.4–39.5 for the UCL for *cis/trans*-DCCA and 3-PBA, considering $k_d$. For participant A4, because the metabolites had less excretion than others, they were 617.0–861.6 for *cis/trans*-DCCA and 134.2–196.4 for 3-PBA without considering $k_d$; 304.5–419.8 for *cis/trans*-DCCA and 68.0–94.7 for 3-PBA considering $k_d$. For the $U_F$ group, the ratios were 2.0–41.5and 3.6–76.6for the LCL and 2.5–32.6 and 3.2–95.6 for the UCL for *cis/trans*-DCCA and 3-PBA without considering $k_d$; 1.7–31.4and 2.6–73.6for the LCL and 2.1–40.6and 3.0–91.8for the UCL for *cis/trans*-DCCA and 3-PBA considering $k_d$. Participant B10 reported a longer product use time, they were 2409.7–3531.4 for *cis/trans*-DCCA and 2943.2–3689.2 for 3-PBA without considering $k_d$; 108.5–136.0 for *cis/trans*-DCCA and 75.3–95.3

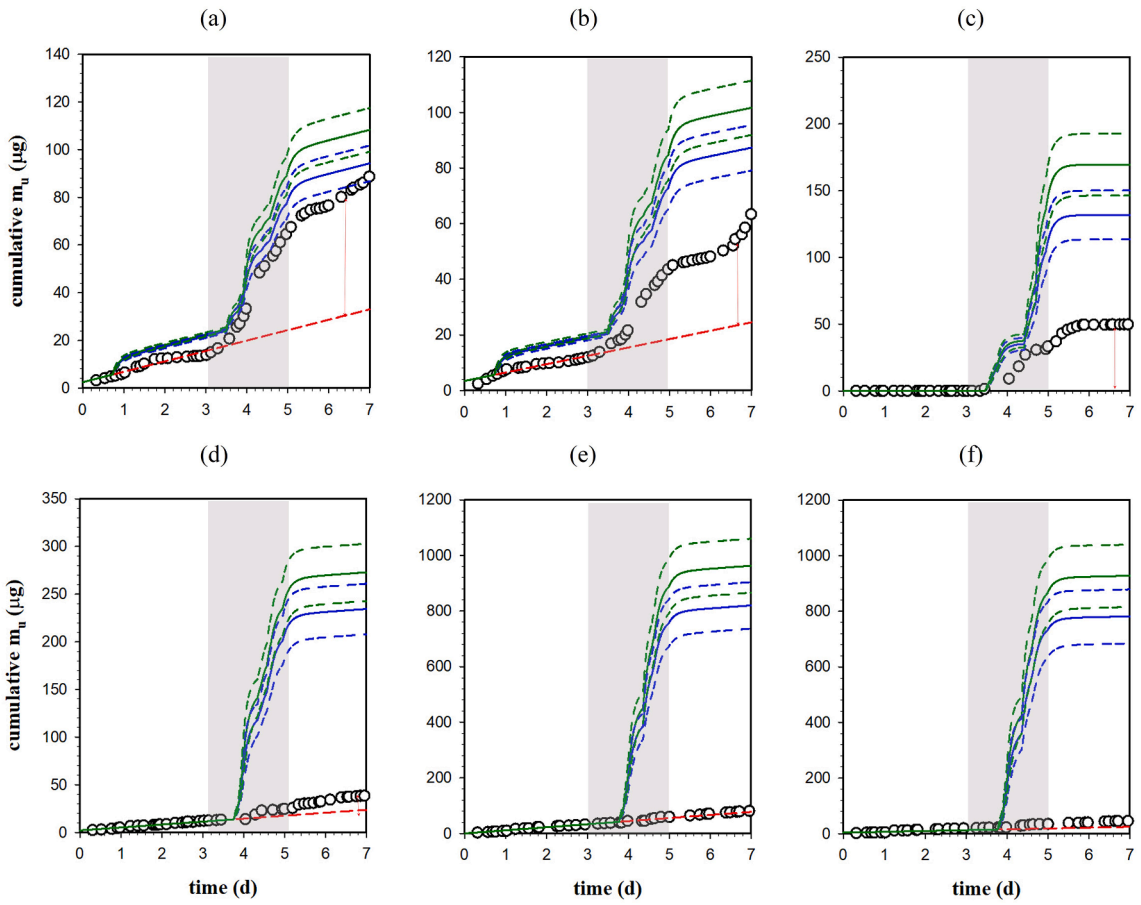


**Fig. 3.** Cumulative mass of *cis/trans*-DCCA (a, c, e), and 3-PBA (b, d, f) in urine during the intervention study (7 d) with an intervention effect for A1 (a, b), with an intervention effect and no background excretion of *cis/trans*-DCCA for A2 (c, d), and without an intervention effect for A6 (e, f). The circle shows the measured molar masses of *cis/trans*-DCCA, and 3-PBA. Green lines present the estimated cumulative amount of urinary excretion using the model without considering $k_d$ and blue lines considering $k_d$. Dashed lines indicate the upper and the lower 95% confidence limits (UCLs and LCLs) obtained by a Monte-Carlo simulation (n = 125). Red dashed lines present the background excretion based on the average excretion during period 1. The shaded areas indicate the intervention period. Red arrow indicates the intervention effects. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for 3-PBA considering $k_d$, thereby resulting in much higher model predictions. All other values are shown in Tables S11and S12.

## 4. Discussion

### 4.1. Exposure to permethrin via household insecticide use

The excretion of 3-PBA and *cis/trans*-DCCA is common for people who are exposed to various pyrethroids from diverse sources, including food (ATSDR, 2003; Barr et al., 2010; Li and Kannan, 2018; Quindroit et al., 2019; Schettgen et al., 2002). In this study, it was not possible to estimate the contribution of food to the excretion of 3-PBA and *cis/trans*-DCCA over the test period, as pyrethroid exposure from diet was not determined. Although the linear slope of excretion (Figs. 1 and 3 and Tables S7 and S8) varied among participants, it was rather constant over period 1 for a given participant. This made it possible to evaluate the effects of heavy home insecticide use during the summer season, as discussed below.

For *cis/trans*-DCCA and 3-PBA, some participants had an intervention effect, and the $U_{24h}$ group exhibited a more distinct intervention effect than the $U_F$ group. Although the experiment was designed based on the average levels of permethrin metabolites (MFDS, 2009), individual variations were large enough that the intervention effects were not observed for some participants. In the $U_F$ group, metabolite excretion could not be reflected in the $U_F$ of the day owing to the short half-life of permethrin (ATSDR, 2003). It was difficult to find any specific differences between participants with and without intervention effects in the daily journals. Individual chemical monitoring at the place of application may better explain the differences between the two groups.

### 4.2. Estimation of potential risks of home insecticide sprays

For all participants, except for A1, the total amount of urinary excretion of 3-PBA and *cis/trans*-DCCA was less than that predicted using the model (Fig. 3 and S2). Thus, this simple exposure model is promising for the initial screening exposure estimation of spray-type home insecticides, including pyrethroids, because it rarely underestimate the exposure to permethrin. The differences between the model predictions and measurements represented by $UE_{pred}/UE_{meas}$ varied for all participants (Tables S11 and S12). The high variability in $UE_{pred}/UE_{meas}$ might be explained by: (1) uncertainties associated with the micro-environmental distribution of permethrin in the exposure zone, such as deposition and partitioning to dust particles (Berger-Preiß et al., 1997; Matoba et al., 2004; Clausen et al., 2020); (2) uncertainties in personal behavior after spraying; (3) experimental uncertainties with normalization of metabolite excretion based on creatinine; (4) single exposure parameter values such as the air change rate with or without ventilation (Wallace et al., 2002); and (5) physiological variations in absorption, distribution, metabolism, and excretion processes among participants (Fendinger and Glotfelty, 1990; Hu and Leng, 1992); and (6) uncertainties due to the use of single exposure parameter values in modeling.

Berger-Preiß et al. (1997) measured the distribution of pyrethroids in air, suspended particles, dust, and furniture surfaces when using spray-type consumer products in a model house. They detected small amounts of pyrethroids in the air and relatively large amounts in other media because permethrin readily sorbed to furniture surfaces in the model house after the application of the spray and remained on the surfaces for 12 weeks. Similarly, Matoba et al. (2004) conducted a floor residue test using an electric vaporizer containing prallethrin and showed that 2.7% of prallethrin remained on the floor after 12 h. The log octanol–water partition constant of permethrin is 6.67 (Hu and Leng, 1992) and its Henry's law constant is 0.0867 $Pa{\cdot}m^3{\cdot}mol^{-1}$ (Fendinger and Glotfelty, 1990), thereby suggesting low volatility and significant sorption to various indoor surfaces. In this study, the $k_d$ value (2.8 $h^{-1}$) measured by Clausen et al. (2020) in a controlled climate chamber (20.3 $m^3$) was applied. As shown in Fig. 3 and S2, the inclusion of $k_d$ fills some gaps between the predicted and measured excretion of permethrin metabolites. However, a single $k_d$ value is insufficient for various exposure conditions in different participants, and individual air monitoring could better explain variations among participants.

Although participants were instructed to fill out the exposure conditions (time of product use, time of exposure, and place of exposure) in their daily journal, the exposure patterns were different (exposure pattern, usage pattern, and space they preferred to stay). The uncertainties in the movement patterns of the participants after use might have affected the atmospheric concentration in the exposure zone.

The air change rate in the place of application was assumed from the values suggested by NIER (2014). Because the volume and air conditioning or ventilation systems were different for participants, it is expected that there would be large variations in the air change rate (Bremmer et al., 2006) and the Monte Carlo simulation partly explained these variations. Opening windows is also an important factor in the air change rate. The width of the opening of a window affects the air change rate (Howard-Reed et al., 2011). Although the size of the windows was different in houses and rooms and the width of the opening varied during the experiment, we used a single average parameter (Wallace et al., 2002).

The fraction of permethrin absorbed via inhalation was not clearly reported. The absorbed fraction of permethrin could be vary depending on its distribution between dust particles and air and the absorption fraction for individual participants might be different from the 70% absorption assumed in this study (Egeghy et al. 2011).

## 5. Conclusions

The importance of home insecticide spray during the summer season was evaluated for a model pyrethroid, permethrin, using biomonitoring and personal exposure modeling for 27 consumer participants. Significant increase in the levels of metabolites, 3-PBA and *cis/trans*-DCCA, in 15 consumer participants after the application of home insecticide products supports that the heavy use of home insecticides during summer could be an important exposure route. In addition, the predicted levels of metabolites using a personal exposure model were consistently greater than those analyzed in the urine samples, suggesting that the rapid loss of permethrin after application could explain the differences. Although a certain degree of overestimation of exposure is expected when the model is used for screening risk assessment of pyrethroids, the model performance would be acceptable considering a safety margin.

## CRediT authorship contribution statement

**Seon-Kyung Park:** Conceptualization, Data curation, Software, Methodology, Investigation, Writing - original draft. **Heon-Jun Lee:** Data curation, Methodology, Investigation, Writing - original draft. **Eugene Song:** Data curation, Investigation. **Yoonsub Kim:** Data curation, Investigation. **Du Yung Kim:** Data curation, Investigation. **Jong-Hyeon Lee:** Conceptualization, Funding acquisition. **Hyun Jung Yoo:** Supervision, Funding acquisition. **Jeong-Eun Oh:** Conceptualization, Supervision. **Jung-Hwan Kwon:** Conceptualization, Methodology, Supervision, Writing - review & editing.

## Declaration of Competing Interest

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

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106581.

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