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Pyrethroids in indoor air during application of various mosquito repellents: Occurrence, dissipation and potential exposure risk

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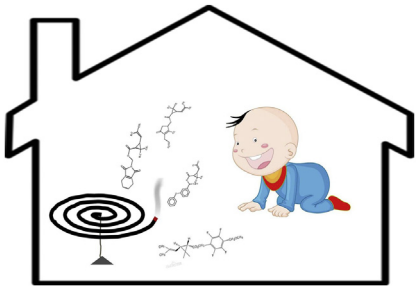
HIGHLIGHTS

- The types of mosquito repellents (MRs) affected indoor exposure to pyrethroids.
- Pyrethroid levels increased 3–6 orders of magnitude after indoor MR application.
- The gas-particle partitioning and dissipation of pyrethroids varied among MRs.
- Vaporizing mat-emitted allethrin posed significant risk to children (<6 years old).

GRAPHICAL ABSTRACT



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ABSTRACT

Commercial mosquito repellents (MRs) are generally applied as mosquito coils, electric vaporizers (liquid and solid) or aerosol spray, with pyrethroids often being the active ingredients. Four types of MRs were applied individually in a 13-m^2 bedroom to study the occurrence, dissipation and risk of pyrethroids in indoor environments. Total air concentrations (in gas and particle phases) of allethrin, cypermethrin, dimefluthrin and tetramethrin during MR applications were three to six orders of magnitude higher than indoor levels before the applications, and allethrin emitted from a vaporizing mat reached the highest concentration measured during the current study (18,600 ± 4980 ng m^{-3}). The fate of airborne pyrethroids was different when the four MRs were applied. Particle-associated allethrin accounted for 95% of its total concentration from the aerosol spray, and was significantly higher than the vaporizing mat (67%), suggesting that the released phase of MRs and size distribution of pyrethroid-carrying particles played important roles in the gas-particle partitioning process. In addition, air exchange through open windows more effectively reduced the levels of indoor pyrethroids than ventilation using an air conditioner. The inhalation risk quotients (RQ) for allethrin derived from application of the vaporizing mat ranged from 1.04 ± 0.40 to 1.98 ± 0.75 for different age-subgroups of the population, suggesting potential exposure risk. Special attention should be given concerning indoor exposure of pyrethroids to these vulnerable groups.

1. Introduction

Indoor air pollution and its toxicological effects have become a growing concern, since humans spend more than 80% of their

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time in indoor environments, where they are potentially exposed to a variety of xenobiotics, e.g., insecticides (Hadnagy et al., 2003; Zhang et al., 2013). The increased use of insecticides in homes for pest control has drawn extra attention to the risk of indoor exposure to these substances (Davis and Ahmed, 1998; Yusà et al., 2014; Zhang et al., 2014). Specifically, spraying of insecticides at high levels has been recommended as an emergency vector-control practice during outbreaks of mosquito-borne illnesses, e.g. dengue fever, in subtropical countries (http://www.who.int/mediacentre/factsheets/fs117/en/); however, this practice may cause considerable exposure of humans to these insecticides (Jin et al., 2015; Zhang et al., 2013). Meanwhile, modern homes are often designed to be more airtight compared with older construction to improve energy efficiency. As a result, these buildings tend to have lower ventilation rates, which decreases the dispersion of indoor contaminants, thereby increasing the risk of indoor exposure (Jones, 1999; Keig et al., 2014; Zhang et al., 2013).

Synthetic pyrethroids are widely used as active ingredients in mosquito repellents (MR) owing to their relatively low toxicity to mammals (Narendra et al., 2008; Pauluhn, 1999; Vesin et al., 2013). Recent studies, however, showed that pyrethroids might cause behavioral and developmental neurotoxicity, with special concern revolving around infants and children, due to their potential exposure during a sensitive neurodevelopmental stage (Shafer et al., 2005). In addition, some pyrethroids are listed as endocrine disruptors and possible carcinogens (USEPA, 2006; Vesin et al., 2013).

Long-term exposure to pyrethroid-based MRs in indoor environments has been shown to cause chronic neurotoxicity, e.g. dysfunction of blood–brain barrier permeability, oxidative damage to the brain (Gupta et al., 1999; Sinha et al., 2004), and cholinergic dysfunction leading to learning and memory deficiencies (Sinha et al., 2006). Wu et al. (2013) assessed indoor exposure of pyrethroids in China using questionnaires and measured urinary levels of pyrethroid metabolites in infants, and found that application of MRs significantly increased levels of urinary metabolites. On the other hand, direct indoor exposure data, including air concentrations of pyrethroids during and immediately after MR application are limited. In one of the few studies examining this issue, Vesin et al. (2013) detected elevated concentration of transfluthrin in the gaseous phase during the indoor application of an electric vaporizer, but they found inhalation risk of airborne transfluthrin was low. The exposure levels and potential risk of pyrethroids during the applications of other types of commonly used MRs remain unknown.

The objectives of the current study were to evaluate the occurrence, dissipation and potential risk of pyrethroids in indoor air induced by the use of four pyrethroid-based MRs, including a traditional mosquito coil, two electric vaporizers (liquid vaporizer and vaporizing mat) and an aerosol spray. Specific objectives included (1) monitoring indoor air concentrations of the active ingredient pyrethroids during and immediately after the individual application of various MRs, (2) evaluating the partitioning of pyrethroids between gas and particle phases and the dissipation of indoor airborne pyrethroids, and (3) quantitatively estimating the risk from potential exposure to the indoor application of pyrethroid-based MRs.

2. Materials and methods

2.1. Pyrethroid-based MRs, chemicals and reagents

Four types of MRs that are distributed under the brand name Raid® were used in the current study and included a mosquito coil, liquid vaporizer, vaporizing mat and aerosol spray. The MRs were purchased from a local supermarket in Guangzhou, China. Descriptions of the MRs and their active ingredients, as well as the application procedures are detailed in Table S1 in the Supplementary material ("S" represents figures and tables in the Supplementary material thereafter).

Neat standards of pyrethroids (allethrin, cypermethrin, dimefluthrin and tetramethrin), which were the active ingredients in the MRs, were obtained from ChemService (West Chester, PA, USA) and had purities >97% as indicated by the manufacturer. Decachlorobiphenyl and 4,4′-dibromooctafluorobiphenyl (Supelco, Bellefonte, PA, USA) were used as the surrogates to check the performance of sample preparation procedures, and *trans*-cypermethrin-d_6 (Dr. Ehrenstorfer GmbH, Germany) was used as the internal standard for quantifying the target pyrethroids on gas chromatography/mass spectrometry (GC/MS). Hexane was high performance liquid chromatography grade and was purchased from Burdick and Jackson (Burdick and Jackson, Korea), while dichloromethane and acetone (analytical grade) were purchased from Tianjin Chemical Reagent Factory (Tianjin, China) and were redistilled prior to use. Copper sheets were activated using concentrated HCl, and sequentially washed with distilled water and acetone. Primary secondary amine (PSA) and graphitic carbon black (GCB) were purchased from Agela Technologies (Wilmington, DE, USA) and Strem Chemicals (Newburyport, MA, USA), respectively. Anhydrous Na_2SO_4 was baked at 450 °C for 4 h prior to use.

2.2. Room description and air sampling

Air sampling was carried out in a single bedroom of a standard sized apartment in the Guangzhou Institute of Geochemistry, Chinese Academy of Sciences (GIGCAS) in China. The 13-m^2 bedroom had a volume of 36.2 m^3 and was furnished with a bed, a wardrobe, and two tables. The mosquito coil, liquid vaporizer, and vaporizing mat were placed on the floor close to the bed for use, while aerosol spray was applied towards the corners of the bedroom for 6 s according to the labeled instructions. The four types of MRs were sequentially applied at night in the same bedroom for three continuous nights for each MR. The dates for MR applications are listed in Table S1.

During the application period of the MRs (from 20:00 to 8:00 of the next day), indoor air was sampled using a high-volume active sampler (Laoshan Electronic Instrument, Qingdao, China) at a velocity of 0.5 $m^3\ h^{-1}$. The sampler was placed 1 m away from the MRs. A polyurethane foam plug (PUF) and a glass fiber filter (GFF, Whatman, Maidstone, England) in the sampler served to collect pyrethroid in the gas and particle phases, respectively. The PUF had a diameter of 6.5 cm, a thickness of 8.0 cm and a density of 0.03 g cm^{-3} and was purified by sequential sonication with methanol and dichloromethane three times each and then dried at room temperature before use. The GFF had an area of 20.3 × 25.4 cm^2 and a pore size of 0.6 μm, and was baked at 450 °C for 4 h prior to use. The PUF and GFF were located on the top of the sampler and were 1 m above the floor. At the termination of the MR application at 8 o'clock, the PUF and GFF were removed from the sampler and fresh PUF and GFF were added to conduct an additional 12 h of sampling after application of MRs (8:00 to 20:00). After sampling, the PUF and GFF were wrapped individually with clean aluminum foil, sealed in plastic bags, transferred back to the laboratory and stored at −20 °C.

To investigate the influence of indoor–outdoor air exchange on the fate of airborne pyrethroids, two scenarios were considered (Table S1). In the first scenario, the window of the bedroom was closed and the air conditioner was turned on, while the other scenario involved keeping the window open and the air conditioner was turned off. The room temperature was kept constant at 25 °C

when the window was closed, and the air temperature was monitored at 15–16 °C during the air sampling with the window open. In the room with closed window, the MR applications were performed sequentially in the order of vaporizing mat, mosquito coil, liquid vaporizers and aerosol spray. Only the mosquito coil was used in the room with an open window.

2.3. Sample preparation

The PUFs and GFFs were wrapped in a filter paper cylinder and extracted in a Soxhlet extractor for 48 h. A mixture of 200 mL of hexane: dichloromethane: acetone (2:2:1, v/v/v) was used as the extraction solvents. Before extraction, two surrogates, decachlorobiphenyl and 4,4′-dibromooctaflurobiphenyl, were added to all the samples and several pieces of copper sheets were also added to remove residual sulfur in the samples. After extraction, the extracts were concentrated and solvent exchanged to hexane using a Turbovap (Xintuo, Shanghai, China).

The extract was cleaned using a column packed with 600 mg of PSA, 300 mg of GCB and 2 g of anhydrous Na_2SO_4 from the bottom to the top. Six milliliters of hexane was added to precondition the column. After loading the sample, 9 mL of a mixture of hexane and acetone (1:1, v/v) was used to elute the target pyrethroids from the column. The cleaned extract was concentrated, solvent exchanged to hexane, and analyzed on GC/MS after adding the internal standard.

2.4. Instrumental analysis

Pyrethroids were quantified on a Shimadzu QP-2010-plus series GC/MS (Shimadzu, Japan) in negative chemical ionization (NCI) mode. A DB-5HT column (15 m × 0.25 mm, 0.1 μm film thickness) was used to separate the analytes. Helium was used as the carrier gas at a flow rate of 1.5 mL min^{-1}, and methane was used as NCI reaction gas. The temperature of ion source and transfer line was set at 250 and 280 °C, respectively. The oven temperature started at 60 °C, held for 1 min, heated to 200 °C at 10 °C min^{-1}, to 220 °C at 3 °C min^{-1}, held for 8 min, then heated to 300 °C at 50 °C min^{-1}, and finally held for 15 min. A programmable temperature vaporizing injector was used to inject 1 μL of extract into the GC/MS and the initial injector temperature was set at 60 °C, held for 0.1 min, and then ramped to 280 °C at 300 °C min^{-1}, and held for 17 min. Qualification of the analytes was based on the detection of target and qualifier ions within a retention time window of 1%. To minimize the matrix effects during GC quantification, matrix-matched calibration standards were used with *trans*-cypermethrin-d_6 being the internal standard (Wang et al., 2010).

2.5. Quality assurance and quality control

Four types of QA/QC samples were processed simultaneously with every 20 samples and included a solvent blank (filter paper cylinder only), a matrix blank (a clean PUF or GFF wrapped in a filter paper cylinder), a matrix spike and its duplicate (a PUF or GFF spiked with target pyrethroids and wrapped in a filter paper cylinder). No analytes were found in the solvent blanks. Cypermethrin and tetramethrin were not detected in any of the laboratory blanks, while allethrin and dimefluthrin were found in some of the PUF blanks, with their concentrations on an air basis ranging from less than reporting limit (<RL) to 0.91 ng m^{-3} and from non-detected (ND) to 0.026 ng m^{-3}, respectively. The recoveries of the four pyrethroids in the matrix spikes were from 60% to 149%. The recoveries of the two surrogates, 4,4′-dibromooctaflurobiphenyl and decachlorobiphenyl were 94 ± 25% and 102 ± 27%, respectively. Furthermore, the instrument was regularly checked by analyzing a calibration standard every 10 samples and the variations of individual analytes were lower than 20%.

2.6. Data analysis

Concentrations of the target pyrethroids in indoor air due to different MR treatments were compared using a *t*-test and a *p* value of <0.05 indicated significant difference.

The potential inhalation exposure ($PE_{inhalation}$, ng kg^{-1} d^{-1}) of the pyrethroids during applying the MRs was calculated using the following equation (Schleier III et al., 2009).

$$PE_{inhalation} = \frac{C_{total} \times RR \times D}{BW} \quad (1)$$

Where, C_{total} was the total air concentration (ng m^{-3}) of the target pyrethroid in gas and particle phases, *RR* was the respiratory rate (m^3 h^{-1}), *D* was the duration of exposure (h d^{-1}) and 8 h d^{-1} was the recommended duration of exposure for risk assessments during application of MRs indoors (Vesin et al., 2013), and *BW* was body weight (kg). To evaluate age-related exposure, six subgroups of the population were included in the assessments: infants (0–1.5 years old), toddlers (1.5–3 years old), children (3–6 years old), youth (10–12 years old), and adult males and females (18–65 years old). The respiratory rates and body weights for the subgroups were obtained from the literature (Brochuab et al., 2006; Portier et al., 2007) (Table S2). The risk quotient (RQ) was calculated by dividing the *PE* of a pyrethroid to its inhalation reference dose (RfD). The RfD was estimated from the no observed adverse effect level (NOAEL) in mammals using an appropriate safety factor recommended by the USEPA (Schleier III et al., 2009; USEPA, 2006, 2009). The long-term inhalation NOAEL values for allethrin and cypermethrin were 1.3 and 2.7 mg kg^{-1} d^{-1}, respectively, with the respective safety factors being 1000 and 300. Therefore, the calculated RfD values for allethrin and cypermethrin were 0.0013 and 0.009 mg kg^{-1} d^{-1}, respectively (USEPA, 2006, 2009). The RfD values for dimefluthrin and tetramethrin were not available.

At the meantime, the potential exposure via non-dietary ingestion ($PE_{ingestion}$), dermal-dust adherence ($PE_{dermal\text{-}dust}$) and dermal-gas absorption ($PE_{dermal\text{-}gas}$) of the pyrethroids during the application of the MRs were also estimated for infants, toddlers and children using the following equations (Gaspar et al., 2014).

$$PE_{ingestion} = \frac{C_{dust} \times IGR \times D}{BW} \quad (2)$$

$$PE_{dermal-dust} = C_{dust} \times SABW \times AE \times A \times ABS \times D \quad (3)$$

$$PE_{dermal-gas} = C_g \times K_{p-g} \times SABW \times D \quad (4)$$

$$C_{dust} = \frac{C_g \times K_{OA} \times f_{om-dust}}{\rho_{dust}} \quad (5)$$

$$PE_{total} = PE_{inhalation} + PE_{ingestion} + PE_{dermal-dust} + PE_{dermal-gas} \quad (6)$$

Where, C_{dust} and C_g were the concentrations of pyrethroids in the indoor settled dust and gas phases of air, respectively, *IGR* was the ingestion rate of indoor settled dust, and *SABW* was the ratio of body surface area to body weight. The *AE* was the fraction of body surface area exposed and a value of 0.3 ± 0.1 was used (USEPA, 2011), *A* was the total dust adhered to the body and 0.04 ± 0.001 g m^{-2} was used (USEPA, 2011), and *ABS* was the dermal absorption fraction and 0.1 ± 0.07 was used (OEHHA, 2012). The indoor air transdermal coefficients ($K_{p\text{-}g}$) for

the target pyrethroids were unavailable, and thus $K_{p\text{-}g}$ value of permethrin (112.8 m d^{-1}, Weschler and Nazaroff, 2012) was used for the calculations. The K_{OA} was the partition coefficient between octanol and air and the values were obtained from KOAWIN v1.10 estimation. In addition, $f_{om\text{-}dust}$ and ρ_{dust} were the volume fraction of organic matters and density of the settled dust, and 0.2 and 2.0×10^6 g m^{-3} were used as suggested by Weschler and Nazaroff (2010), respectively.

A Monte-Carlo simulation was applied to evaluate the uncertainty and sensitivity of potential exposure and RQs using Crystal Ball 11.1 at 20,000 randomizations.

3. Results and discussion

3.1. Occurrence of pyrethroids in indoor air during MR applications

As shown in Table S1, allethrin, cypermethrin, dimefluthrin and tetramethrin were the active ingredients in the MRs studied, and their total air concentrations (particle and gas phases combined) before MR application in the room were 0.042 ± 0.028, 0.033 ± 0.039, 0.0096 ± 0.0028 and 0.052 ± 0.094 ng m^{-3}, respectively. The use of MRs markedly increased the concentrations of pyrethroids in the indoor air, with the concentrations being three to six orders of magnitude greater than the levels before MR application (Fig. 1 and Table S3). The total concentrations of dimefluthrin, the active ingredient in the mosquito coil, were 526 ± 33 and 573 ± 181 ng m^{-3} when the coils were burned in the room with the window open and closed, respectively. The air concentration of dimefluthrin was 272 ± 77 ng m^{-3} when the liquid vaporizer was used. Allethrin was the active ingredient in the vaporizing mat and its air concentration was 18,600 ± 4980 ng m^{-3} during its application. The aerosol spray was different from the other MR treatments in that it contained a mixture of allethrin, cypermethrin and tetramethrin, and their concentrations in air 12 h after spraying were 215 ± 51, 28.4 ± 7.2 and 32.1 ± 15.9 ng m^{-3}, respectively.

The occurrence of pyrethroids in indoor air in the current study was compared to previous studies reporting indoor air concentrations of pyrethroids due to the application of MRs (Table 1). Pyrethroid concentrations during application of electric vaporizers (liquid vaporizer and vaporizing mat) measured in the current study were comparable to the results in several studies (Class and Kintrup, 1991; Nazimek et al., 2011; Vesin et al., 2013), but were orders of magnitude lower than the concentrations reported by Ramesh and Vijayalakshmi (2001). In the case of the aerosol spray, indoor air concentrations of active ingredient pyrethroids in the current study were much lower than those reported in other studies (Class and Kintrup, 1991; Ramesh and Vijayalakshmi, 2001). The differences in the amount of spray being used and sampling duration after the spray were the likely reasons for the variation in pyrethroid concentrations reported among studies. As shown in Table 1, different sampling durations were used, i.e., instantaneous concentrations at a specific time point and/or the time weighted average concentrations of 4, 6 and 12 h during application of the MRs. Specifically for the aerosol spray, spray time directly affected the amount of active ingredient that was emitted into the air and it varied between studies (6 s in the current study and 10–20 s in the study by Class and Kintrup (1991)). Berger-Preiß et al. (2009) monitored airborne concentrations of indoor insecticides during a worst-case application of aerosol spray with a spraying time of 120 s, and found that the air concentration of tetramethrin reached as high as 3220 μg m^{-3}, suggesting considerable potential exposure risk to humans.

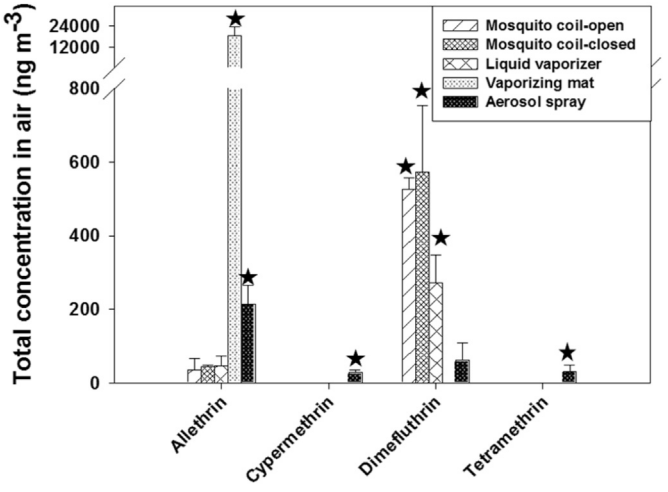

Fig. 1. The total concentrations (gas and particle phases combined) of allethrin, cypermethrin, dimefluthrin and tetramethrin in indoor air during application of the mosquito repellents. Error bars represent the standard deviation of pyrethroid concentrations of each mosquito repellent ($n = 3$). The asterisk indicates that the pyrethroid was the active ingredient of the corresponding mosquito repellent.

In addition, airborne concentrations of pyrethroids during the indoor application of MRs were over orders of magnitude higher than those in the outdoor air (Li et al., 2014). For example, indoor air concentration of allethrin during application of the vaporizing mat was six orders of magnitude higher than that outdoors, implying high occurrence of pyrethroids in the indoor environments due to application of the MR (Li et al., 2014).

3.2. Gas-particle partitioning of pyrethroids during the MR applications

Distribution of pyrethroids between gas and particle phases was one of the critical factors affecting their fate and behavior after being emitted into air during the application process. This distribution then influenced the route and extent of potential human exposure to these contaminants (Ramesh and Vijayalakshmi, 2002; Sanusi et al., 1999). In general, particle-associated pyrethroids are more easily deposited on various surfaces, while gaseous compounds have a greater tendency to remain in the air (Matoba et al., 2004; Vesin et al., 2013). The gas-particle partitioning of pyrethroids in indoor air during (at night) and after (during the daytime) application of the MRs is presented in Fig. 2. The percentage of pyrethroids in particles compared to the total concentrations in gas and particle phases were not statistically different during and after the MR application (Fig. 2), therefore, only the partitioning of the pyrethroids at night will be discussed. On average, 42% and 37% of dimefluthrin was associated with particles when the mosquito coil was used with the window open and closed, respectively, and the value was 41% when the liquid vaporizer was used. Similarly, 68% of allethrin emitted from the vaporizing mat was associated with particles. Conversely, the majority of allethrin, cypermethrin and tetramethrin due to the use of the aerosol spray were associated with particles, with average percentages of 95%, 98% and 94%, respectively.

To our knowledge, no studies have reported indoor gas-particle partitioning of pyrethroids, so the partitioning behavior of pyrethroids during the MR applications in the current study were compared instead to outdoor partitioning data. Li et al. (2014) found that allethrin and dimefluthrin were almost equally distributed between gas and particle phases in outdoor air in South China, which was consistent with the indoor composition of these two pyrethroids through the application of the mosquito coil and electric vaporizer as part of the current study. Nevertheless, a confounding situation was noted when the aerosol spray was applied indoors. Vapor pressure is considered an important property

Table 1
Indoor air concentrations of pyrethroids during and after the application of pyrethroid-based mosquito repellents (MR) in different studies.

MR type	Active ingredient	Content	Volume of test room (m^3)	Air concentration (during application)	Air concentration (after application)	Reference
Mosquito coil	Allethrin	0.1% (w/w)	26.2	<0.1–8.1 mg m^{-3}		Ramesh and Vijayalakshmi, 2001[a]
	Dimefluthrin	0.012% (w/w)	36.2	503–549 ng m^{-3} (window open) 454–781 ng m^{-3} (window closed)	0.01–0.1 ng m^{-3} (window open) 34.4–45.8 ng m^{-3} (window closed)	The current study[b]
	Transfluthrin	0.03% (w/w)	26.2	<0.1–13.4 mg m^{-3}		Ramesh and Vijayalakshmi, 2001
Liquid vaporizer	Dimefluthrin	0.62% (w/w)	36.2	193–346 ng m^{-3}	116–181 ng m^{-3}	The current study
	Transfluthrin	0.88% (w/w)	32.3	5.6 μg m^{-3}		Vesin et al., 2013[c]
		37.50%	46.7	1290–2420 ng m^{-3}		Nazimek et al., 2011[d]
Vaporizing mat	Allethrin	50 mg/piece	36.2	15,100–24,300 ng m^{-3}	310–1570 ng m^{-3}	The current study
		25 mg/piece	50	2.5 (2–5) μg m^{-3} (average)	<1 μg m^{-3}	Class and Kintrup, 1991[e]
	Prallethrin	1.5% (w/w)	26.2	<0.1–13.8 mg m^{-3}		Ramesh and Vijayalakshmi, 2001
	Transfluthrin	13.4% (w/w)	32.3	4.9–8.5 μg m^{-3}		Vesin et al., 2013
Aerosol spray	Allethrin	0.13% (w/w)	26.2	<0.1–80 mg m^{-3}		Ramesh and Vijayalakshmi, 2001
		0.1% (w/w)	36.2	170–271 ng m^{-3}	20.9–74.4 ng m^{-3}	The current study
	Cyfluthrin	0.27% (w/w)	50	10–90 μg m^{-3}		Class and Kintrup, 1991
	Cypermethrin	0.15% (w/w)	36.2	21.7–36.0 ng m^{-3}	0.46–0.61 ng m^{-3}	The current study
	Deltamethrin	0.02% (w/w)	26.2	<0.1–5.7 mg m^{-3}		Ramesh and Vijayalakshmi, 2001
	Tetramethrin	0.9% (w/w)	50	45–300 μg m^{-3}		Class and Kintrup, 1991
	Transfluthrin	0.3% (w/w)	36.2	16.5–48.3 ng m^{-3}	2.4–9.5 ng m^{-3}	The current study

[a] The reported concentrations were the instantaneous concentrations at a specific time point during the application of the MRs.
[b] The reported concentrations were the 12-h time weighted average (TWA) concentrations during the application of the MRs and the 12-h TWA concentrations after the application of the MRs.
[c] The reported concentrations were the peak concentrations during the application of MRs.
[d] The reported concentrations were the 6-h TWA concentrations during the application of MRs.
[e] The reported concentrations were the 4-h TWA concentrations during the application of MRs.

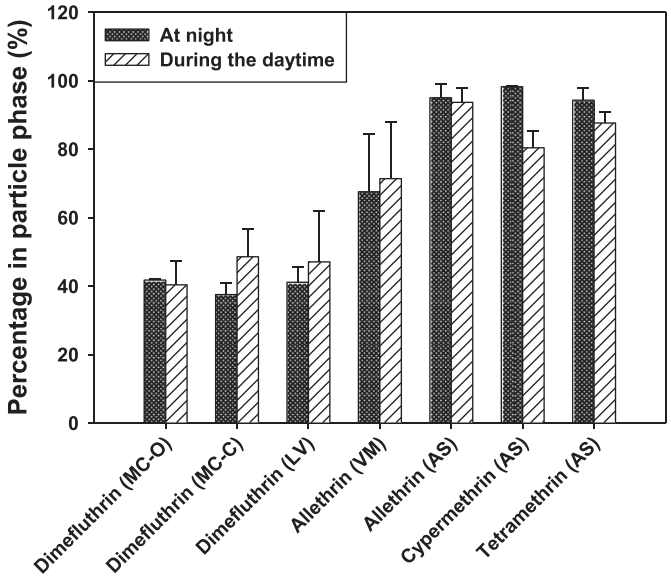

Fig. 2. Percentage of target pyrethroids associated with the particle phase compared to the total air concentrations (gas and particle phases combined) during (at night) and after (during the daytime) application of various mosquito repellents, including a mosquito coil with the window open (MC-O), a mosquito coil with the window closed (MC-C), liquid vaporizer (LV), vaporization mat (VM) and aerosol spray (AS). Error bars represent the standard deviation of the fractions of pyrethroids associated with the particle phase for individual mosquito repellents ($n = 3$). Only the active ingredients of the corresponding mosquito repellents are presented.

governing the partitioning of airborne chemicals, and compounds with lower vapor pressures tend to be associated with the particle phase (Sanusi et al., 1999). Owing to its lower vapor pressure compared with allethrin, dimefluthrin and tetramethrin (Sanusi et al., 1999; Tsuzuki, 2001), cypermethrin was mostly distributed with the particle phase (98% was associated with the particles; Fig. 2), as observed in outdoor air (Li et al., 2014). However, more than 90% of allethrin and tetramethrin during the indoor application of aerosol spray were associated with particles, which was unexpected. Allethrin was the active ingredient for the vaporizing mat and aerosol spray, and exhibited statistically significant differences in gas-particle partitioning behavior when the two MRs were applied (68% and 95% were associated with the particle phase, respectively).

Instead of chemical vapor pressure and environmental parameters (e.g. temperature and humidity, which were the main controlling factors for the partitioning of atmospheric compounds outdoors (Sanusi et al., 1999)), the releasing mode of the active ingredients from the MRs (i.e. gaseous versus particulate phases) governed the distribution of airborne pyrethroids between gas and particle phases in the indoor environments. The size of the indoor particles varied when different MRs were applied (Pauluhn, 2006; Wang et al., 2007; Berger-Preiß et al., 2009). Burning mosquito coils produced smoke, which was composed of particles and gas with active ingredients. The particles emitted from the mosquito coils were mostly submicron aerosol with mass median diameters of 0.5–0.9 μm, which was similar to the background submicron aerosols in indoor and outdoor air (Pauluhn, 2006; Wang et al., 2007). The similar particle sizes of mosquito coil smoke and background air might explain the similar partitioning behavior of dimefluthrin between gas and particle phases indoors and outdoors. Active ingredients in electronic vaporizers were emitted into the air in gaseous phase and then experienced dispersion and partitioning with airborne particles. Therefore, the percentages of particle-bound dimefluthrin and allethrin emitted from the respective liquid vaporizer and vaporizing mat in the indoor environment were similar to those in outdoor air (Li et al., 2014).

Conversely, the particles emitted from the aerosol spray were comparably larger than the background particles. The three-phase

aerosol spraying system used in the current study produced droplets with diameters ranging from 1 to 50 μm, containing a water-in-oil type of emulsion with active ingredients and propellants in organic solvents (Willi and Erwin, 1972). A similar system was characterized by Berger-Preiß et al. (2009) who found that 68% of the droplets from aerosol sprays had diameters ranging from 14 to 46 μm. Active ingredients in aerosol spray were emitted into the air by binding to the droplets, which were two to three orders of magnitude larger than the background airborne particles. Although dispersion occurred in the air, hydrophobic pyrethroids preferred to the water-in-oil droplets, resulting in slower partitioning into the gas phase. Consequently, the majority of allethrin, cypermethrin and tetramethrin were associated with the particle phase after the application of the aerosol spray, regardless of their vapor pressure.

In summary, the key factors affecting the partitioning behavior of pyrethroids indoors were distinct from those outdoors. Vapor pressure and environmental parameters (e.g. temperature) were important factors influencing the distribution of outdoor airborne organic compounds between gas and particle phases. In the case of MR applications in the indoor environment, however, releasing modes of the active ingredients from the MRs also played a key role in gas-particle partitioning of indoor airborne pyrethroids due to the variation in size distribution and composition of the released particles.

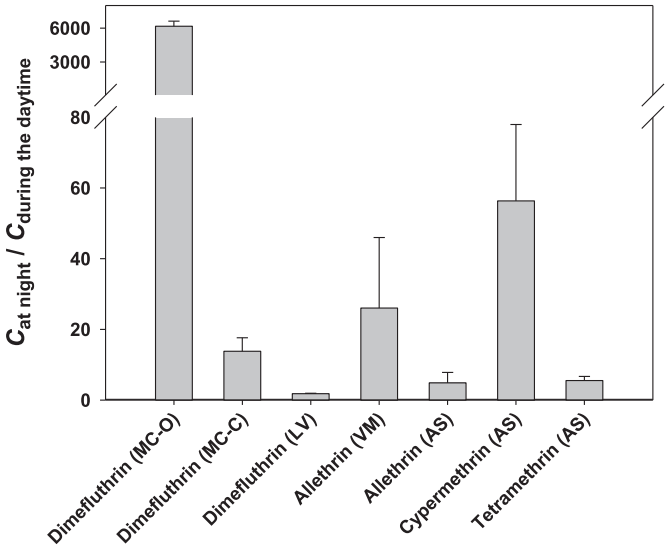

Fig. 3. The dissipation ratios, which were computed as the ratios of total concentrations of pyrethroids (gas and particle phases combined) during (at night) and after (during the daytime) application of various mosquito repellents, including a mosquito coil with the window open (MC-O), a mosquito coil with the window closed (MC-C), liquid vaporizer (LV), vaporization mat (VM) and aerosol spray (AS). Error bars represent the standard deviation of the dissipation rates (n = 3). Only the active ingredients of the corresponding mosquito repellent are presented.

3.3. Dissipation of pyrethroids from the MR application

During and after application of MRs in the indoor environment, emitted active ingredient pyrethroids experienced dispersion, partitioning between gas and particle phases, degradation and deposition. These processes enhanced the dissipation of airborne pyrethroids and subsequently decreased their inhalation exposure risk. Time weighted average concentrations of active ingredient pyrethroids in a period of 12 h after application of the MRs (during the daytime) are presented in Tables 1 and S3. The residues of airborne dimefluthrin after applications of the mosquito coil with the window open, mosquito coil with the window closed, and liquid vaporizer were 0.06 ± 0.04, 41.6 ± 6.3 and 148 ± 32 ng m^{-3}, respectively. The air concentration of allethrin after application of the vaporizing mat was 1050 ± 660 ng m^{-3}, being five orders of magnitude higher than the levels before MR application in the room. The residues of allethrin, cypermethrin and tetramethrin in air during the daytime after application of the aerosol spray were 56.3 ± 30.9, 0.5 ± 0.1 and 6.2 ± 3.6 ng m^{-3}, respectively. The dissipation ratio, which was defined as the ratio of pyrethroid concentrations in air during (at night) and after (during the daytime) application of the MRs, was computed to evaluate the influence of ventilation conditions, chemical properties of the active ingredients, and releasing modes of pyrethroids from the MRs on the dissipation of the pyrethroids in indoor air (Fig. 3).

Ventilation conditions greatly affected the dissipation of airborne pyrethroids. The mosquito coil was applied in the room with natural air exchange (windows open and air condition off) and ventilation created by an air conditioner (window closed and air conditioner on). The indoor air concentrations of dimefluthrin were comparable under both ventilation conditions when the coils were burning. Nevertheless, after the termination of the MR application, airborne residues of dimefluthrin in the room with the window closed were three orders of magnitude higher than that with window open, which quickly dropped to the level before MR application within 12 h (Table S3), and the corresponding mean dissipation ratios for dimefluthrin were 13.8 and 6620, respectively (Fig. 3). Ventilation condition, as well as the different environmental parameters, e.g. temperature and humidity in the room with the window closed and open may have contributed to the difference in dissipation noted for dimefluthrin. Similar results have also been reported in previous studies. For example, the concentration of transfluthrin in the gas phase decreased to the level before MR application within 16 h after removing the electric vaporizers (Vesin et al., 2013). Ramesh and Vijayalakshmi (2002) analyzed residual concentrations of allethrin emitted from mosquito coils on indoor surfaces, and found that allethrin residues in surface dust in a room with the window open were about 10 times lower than that in a closed room. They also found that residual allethrin on the surfaces in the window-open room was completely dissipated within 15 d after the mosquito coil was removed, but residues of allethrin in the closed room still accounted for one third of the concentrations at the point of extinguishment. Although the air conditioner helped to ventilate air in the indoor environment, natural air exchange was significantly better at dissipating the pyrethroids. Thus, it is imperative to open the windows during the daytime after application of the MRs at night.

Since the aerosol spray contained three active ingredient pyrethroids, the impact of chemical properties of the pyrethroids on their dissipation was assessed. As shown in Fig. 3, the dissipation ratio (based on the total air concentrations) of cypermethrin (56.4 ± 21.6) was markedly higher than that of allethrin (4.9 ± 2.9) and tetramethrin (5.5 ± 1.1), and the latter two were not statistically different. Meanwhile, the dissipation ratio of cypermethrin based on the concentration in the particulate phase was about 10 times greater than that on the basis of its gaseous concentration, whereas allethrin and tetramethrin had comparable dissipation ratios in the two phases. So the dissipation of particle-associated cypermethrin dominated the dissipation of cypermethrin from the indoor air, which caused the 10-fold difference in dissipation ratios between cypermethrin and the other two pyrethroids (allethrin and tetramethrin). This was reasonable because cypermethrin has lower vapor pressure and higher tendency to bind to particles than allethrin and tetramethrin.

In theory, the larger an airborne particle, the easier it is for it to be deposited. Thus, it is expected that pyrethroid-carrying par-

ticles from the aerosol spray should experience the fastest deposition among the four studied MRs due to it having the largest particle size. However, the dissipation of airborne allethrin and tetramethrin from the aerosol spray were slower than allethrin from the vaporizing mat and dimefluthrin from the mosquito coil. Other factors, e.g. air concentrations, may influence the dissipation ratio of pyrethroids, however the exact mechanism is still unknown.

3.4. Potential exposure of pyrethroids during MR applications

Potential exposure of six subgroups of humans at different ages was estimated from inhalation of gaseous and particulate pyrethroids during indoor MR applications (Table 2). The potential exposure of different subgroups of the population to pyrethroids ranged from 2.09 ± 0.78 to 2570 ± 986 ng kg^{-1} d^{-1}, with higher exposure levels being noted for infants, toddlers and children compared to youth and adults. The RQs for inhalation exposure of allethrin (from the vaporizing mat), allethrin (from the aerosol spray) and cypermethrin (from the aerosol spray) were 1.04 ± 0.40 to 1.98 ± 0.75, 0.012 ± 0.004 to 0.022 ± 0.008 and (2.31 ± 0.86) × 10^{-4} to (4.38 ± 1.61) × 10^{-4}, respectively, for all of the subgroups. Due to the absence of RfD values for dimefluthrin and tetramethrin, RQs were not estimated for these two compounds. The inhalation risk of allethrin and cypermethrin due to application of the aerosol spray was negligible. Allethrin and tetramethrin are both "first-generation" pyrethroids with similar NOAEL values (USEPA, 2009, 2010), thus the negligible inhalation risk of allethrin from the aerosol spray also implied a negligible risk for tetramethrin from the aerosol spray. In comparison, allethrin emitted from the vaporizing mat had the highest inhalation RQ values among the studied MRs, with mean RQs larger than 1.0 for all the age groups. In addition, the possibility of RQ values exceeding 1.0 were ranging from 47% (adult male) to 96% (infants), implying potential risk to humans via inhalation (Schleier III et al., 2009). Dimefluthrin is a new type of pyrethroid that is mainly used as an active ingredient in MRs, and limited toxicological data are available for this compound making it difficult to assess its relative risk.

Several factors may influence the risk of pyrethroid exposure from MR applications, for example, the gas-particle partitioning of pyrethroids and the composition and size fractions of the emitted particles. Inhalation exposure to airborne contaminants was highly phase-dependent, i.e., contaminants in the gaseous phase and those associated with fine particles could penetrate deeper into lung tissue and subsequently cause more severe damage (Luo et al., 2014). Berger-Preiß et al. (2009) classified the inhalable particulates during application of the aerosol spray and electrovaporizers into three size fractions, including a respirable fraction (inhaled particles that could penetrate the alveoli, ≤5 μm), a thoracic fraction (inhaled particles that could penetrate beyond the larynx, ≤10 μm) and an inhalable fraction (total particles that could be inhaled through the mouth and nose). The authors also found that 19–48% and 59–80% of pyrethroid-carrying particles were in the respirable and thoracic fractions, respectively, suggesting that size distribution of pyrethroid-carrying particles emitted from different MRs significantly influenced the exposure risk via inhalation (Berger-Preiß et al., 2009). As discussed above, allethrin was emitted from the vaporizing mat in the gas phase, and approximately half of the gaseous allethrin was bound to indoor submicron particles; therefore, most of the allethrin emitted from vaporizing mat was in the respirable fraction, resulting in elevated inhalation risk.

Other exposure routes in addition to inhalation (e.g. ingestion) are possible and should also be considered, including ingestion and dermal contact, especially for children who often crawl on the floor and have hand-to-mouth contact with pyrethroid-carrying dust (Vesin et al., 2013; Schleier III et al., 2009). For youth and adults, inhalation exposure of pesticides from ultra-low-volume aerosol applications accounted for 60% of the total exposure; however, this value was only 8% for infants and toddlers to whom exposure from hand-to-mouth contaminant-carrying dust was the major exposure route (60%) and was seven times higher than inhalation exposure (Schleier III et al., 2009). Therefore, in addi-

Table 2
The potential exposure (ng kg^{-1} d^{-1}) through the routes of inhalation, non-dietary ingestion, dermal-dust adherence and dermal-gas absorption to infants (0–1.5 years), toddlers (1.5–3 years) and children (3–6 years) during the application of various mosquito repellents in indoor environment. The data were simulated using Monte Carlo and are presented as mean ± standard deviation.

Exposure route	Age group	Dimefluthrin (MC-O)[a]	Dimefluthrin (MC-C)	Dimefluthrin (LV)	Allethrin (VM)	Allethrin (AS)	Cypermethrin (AS)	Tetramethrin (AS)
Inhalation	Infants 0–1.5 years	73.1 ± 19.5	79.6 ± 33.1	37.7 ± 14.8	2570 ± 986	29.8 ± 10.7	3.95 ± 1.47	4.47 ± 2.55
	Toddlers 1.5–3 years	67.4 ± 15.8	73.3 ± 29.1	34.7 ± 12.8	2380 ± 860	27.6 ± 9.17	3.64 ± 1.24	4.10 ± 2.27
	Children 3–6 years	69.0 ± 14.3	75.1 ± 23.8	35.6 ± 10.1	2440 ± 652	28.2 ± 6.72	3.73 ± 0.94	4.23 ± 2.09
	Youth 10–12 years	57.0 ± 16.1	62.0 ± 26.6	29.4 ± 11.8	2010 ± 787	23.3 ± 8.64	3.07 ± 1.18	3.48 ± 2.05
	Adult females 18–65 years	40.2 ± 9.75	44.1 ± 17.7	20.7 ± 7.65	1420 ± 513	16.4 ± 5.57	2.17 ± 0.76	2.47 ± 1.37
	Adult males 18–65 years	38.7 ± 10.5	42.1 ± 17.7	20.0 ± 7.85	1370 ± 522	15.8 ± 5.7	2.09 ± 0.78	2.36 ± 1.35
Non-dietary ingestion	Infants 0–1.5 years	640 ± 252	756 ± 422	333 ± 155	8620 ± 4780	18.8 ± 21.3	26.8 ± 15.6	0.13 ± 0.06
	Toddlers 1.5–3 years	874 ± 212	1030 ± 466	454 ± 156	11,800 ± 5300	25.5 ± 26.5	39.0 ± 17.1	0.17 ± 0.06
	Children 3–6 years	592 ± 153	700 ± 324	308 ± 109	7990 ± 3690	17.4 ± 18.4	26.5 ± 11.9	0.12 ± 0.04
Dermal-dust adherence	Infants 0–1.5 years	14.7 ± 2.7	17.3 ± 7.3	7.59 ± 2.26	198 ± 83.5	0.44 ± 0.44	0.66 ± 0.26	0.003 ± 0.001
	Toddlers 1.5–3 years	9.63 ± 1.92	11.4 ± 4.88	4.98 ± 1.53	130 ± 55.9	0.29 ± 0.29	0.43 ± 0.18	0.002 ± 0.001
	Children 3–6 years	9.63 ± 1.92	11.4 ± 4.88	4.98 ± 1.53	130 ± 55.6	0.29 ± 0.29	0.43 ± 0.18	0.002 ± 0.001
Dermal-gas absorption	Infants 0–1.5 years	737 ± 135	871 ± 366	381 ± 114	13,200 ± 5560	29.0 ± 29.3	1.20 ± 0.48	3.58 ± 1.12
	Toddlers 1.5–3 years	484 ± 96	572 ± 248	250 ± 77	8670 ± 3720	19.0 ± 19.3	0.79 ± 0.33	2.35 ± 0.76
	Children 3–6 years	484 ± 96	572 ± 248	250 ± 77	8670 ± 3720	19.0 ± 19.3	0.79 ± 0.33	2.35 ± 0.76
The total exposure	Infants 0–1.5 years	1470 ± 299	1730 ± 714	760 ± 232	24,600 ± 9500	77.4 ± 49.1	34.5 ± 16.5	8.19 ± 2.83
	Toddlers 1.5–3 years	1440 ± 247	1690 ± 672	747 ± 212	23,000 ± 8700	72.3 ± 45.3	44.2 ± 17.7	6.67 ± 2.46
	Children 3–6 years	1160 ± 195	1360 ± 529	601 ± 169	19,300 ± 7100	65.0 ± 37.2	31.6 ± 12.5	6.79 ± 2.49

[a] The mosquito repellents included mosquito coil with the window open (MC-O), mosquito coil with the window closed (MC-C), liquid vaporizer (LV) vaporization mat (VM) and aerosol spray (AS).

tion to inhalation, non-dietary ingestion, dermal-dust adherence and dermal-gas absorption were calculated to estimate the total indoor exposure of pyrethroids during application of MRs for infants, toddlers and children as well. The total exposure of vaporizing mat-emitted allethrin for infants, toddlers and children were 24,600 ± 9500, 23,000 ± 8700 and 19,300 ± 700 ng kg^{-1} d^{-1}, respectively. Therefore, the risk of indoor exposure of pyrethroids was related to the type of MRs and allethrin emitted from the vaporizing mat posed potential risk to infants, toddlers and children via inhalation, ingestion and dermal contact.

The contributions of individual exposure routes, including inhalation, non-dietary ingestion, dermal-dust adherence and dermal-gas absorption to the total exposure are presented in Fig. S1. In general, non-dietary ingestion and dermal inhalation were the dominant exposure routes for the three subgroups of humans, except for allethrin and tetramethrin emitted from application of the aerosol spray, which had mean inhalation contributions of 40% and 60%, respectively. The contributions of dermal-dust adherence were low (<2%) in all cases. This finding was similar to Schleier III et al. (2009) that found exposure from hand-to-mouth pyrethroid-carrying dust was the major exposure route for children. More specifically, the contribution of non-dietary ingestion for toddlers was higher than that for infants and children, and it was reasonable, because toddlers are most often crawl around on the floor and have hand-to-mouth contact. The contribution of the four exposure routes for dimefluthrin was comparable among different MR applications, including the mosquito coil (with window open and closed) and liquid vaporizer (A, B and C in Fig. S1), and non-dietary ingestion and dermal-gas absorption were the main routes. The contributions of the exposure routes for allethrin from the vaporizing mat and aerosol spray were distinct from one another (D and E in Fig. S1). For example, the contribution of inhalation for allethrin emitted from the vaporizing mat (~10%) was significantly smaller than that from the aerosol spray (~40%). For the three active ingredients (allethrin, cypermethrin and tetramethrin) emitted from the aerosol spray, the contributions of individual exposure routes were significantly different, suggesting chemical properties of the insecticides were one of the principal factors controlling the contribution of various exposure routes.

In summary, applications of MRs caused elevated airborne concentrations of active ingredient pyrethroids in the indoor environment and posed potential risk to humans, especially infant, toddlers and children who experience more potential routes of exposure and are more susceptible to neurotoxicants at early developmental stages. Although ventilation (i.e., air conditioner and natural air exchange) helped to dissipate airborne pollutants, the persistent residues in air and/or on indoor surfaces could potentially cause continuous exposure to the residents. Moreover, exposure risk of pyrethroids varied markedly for different types of MRs and special attention should be given concerning the risk to infant, toddlers and children to pyrethroid-based vaporizing mats.

Based on the toxicological data from human and animal models, researchers have provided evidence that long-term exposure to pyrethroid-based MRs in the indoor environment can cause chronic neurotoxicity (Gupta et al., 1999; Narendra et al., 2008; Sinha et al., 2004, 2006). In the current study, risk of pyrethroid-based MR applications was quantitatively calculated using exposure data, i.e. airborne concentrations of pyrethroids during application of MRs, and the results provided complementary information to the previous studies which assessed the risk based solely on toxicological data (effects).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.chemosphere.2015.11.025.

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