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Urinary concentrations of permethrin metabolites in US Army personnel in comparison with the US adult population, occupationally exposed cohorts, and other general populations

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ABSTRACT

Permethrin is used to treat clothing as a personal protective measure against insect bites in military and recreational settings, and along with other pyrethroid insecticides, is sprayed in agricultural and residential sites for pest control. The widespread use of permethrin and other pyrethroid insecticides creates a potential for human exposure in occupational and non-occupational populations. This study aims to compare urinary biomarkers of pyrethroid exposure in two US military cohorts to the general US adult population from the 2009–2010 Nutritional Health and Nutrition Examination Survey (NHANES). Additional comparisons are made to previously published biomonitoring data from occupational and population cohort studies.

Urine samples from two US military cohorts were analyzed for 3 permethrin metabolites: 3-phenoxybenzoic acid (3-PBA), and *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (DCCA). Biomarker concentrations were adjusted for creatinine. Geometric means were calculated and then compared to creatinine-adjusted concentrations of 3-PBA and *trans*-DCCA in US adults (aged 20–59) using data collected as part of the 2009–2010 NHANES. Sex- and race-standardized geometric means were calculated separately for each of the US military groups using the demographic distributions from NHANES 2009–2010. Data from other military, occupational, and non-occupational population studies were extracted from the literature for further comparison.

The two US military cohorts' geometric mean values, non-standardized and standardized, were markedly higher than what was observed in the general US adult population. Biomarkers of permethrin exposure were detected at a high frequency in military personnel wearing treated uniforms (90–100%). Detection rates of these biomarkers were similarly high in other studies of occupational exposure (67–100%) to pyrethroid insecticides.

Adjusting for creatinine, the concentrations observed in the military groups were generally higher than levels seen in the general US adult population (NHANES, 2009–2010), other occupational groups (e.g., farmworkers, flight attendants, and pest control workers), and population cohorts from other countries.

1. Introduction

Globally, the use of pyrethroid insecticides is increasing as the use of organophosphate (OP) pesticides decreases (Arcury et al., 2018). Pyrethroid insecticides are neurotoxic to their targets, and the primary mechanism of toxicity is the disruption and alteration of sodium-ion channels in nerve and muscle cells (ATSDR, 2003). However, pyrethroid insecticides are thought to have low mammalian toxicity compared to other classes of pesticides, including OP and carbamate pesticides.

In the United States (US) and Canada, permethrin is the most commonly used pyrethroid (Barr et al., 2010; Health Canada, 2013). Permethrin is used in several different forms to control pests and biting insects. Primarily, it is sprayed on crops in agricultural settings and as an indoor and outdoor residential insecticide (Health Canada, 2013; USEPA, 2009). In occupational and recreational settings, where the potential for exposure to disease-carrying insects exists, permethrin is approved for use as an insecticidal clothing treatment (USEPA, 2009). Other commonly used pyrethroid insecticides include, but are not limited to, cypermethrin, deltamethrin, cyfluthrin, cyhalothrin, fenvalerate, and *d*-phenothrin. The widespread and varied use of pyrethroid insecticides leads to potential human exposure through inhalation,

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ingestion, and dermal routes.

In humans, once pyrethroid insecticides are absorbed, they are quickly metabolized and excreted mainly in the urine. Urinary levels of 3-phenoxybenzoic acid (3-PBA) are used in biomonitoring studies as a biomarker of general pyrethroid exposure. Urinary concentrations of *cis*- and *trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane-1-carboxylic acid (*cis*-DCCA and *trans*-DCCA) are used as biomarkers of exposure to specific pyrethroid insecticides (permethrin, cypermethrin, and cyfluthrin) (Barr et al., 2010). There is a growing body of literature documenting exposure to pyrethroid insecticides using urinary metabolite concentrations as biomarkers of exposure in occupationally and non-occupationally exposed populations.

Permethrin and pyrethroid insecticide exposure have been documented in several occupations, including the agricultural sector, pest control activities, commercial airline industry, as well as textile manufacturing and forestry management. The specific type of pyrethroid and primary route of exposure differs depending on occupation, specific job activities, and seasonal work (Arcury et al., 2018; Ferland et al., 2015; Hardt and Angerer, 2003; Wang et al., 2007). In agriculture, pest control, and the airline industry, a wider range of pyrethroids are often used in addition to permethrin. Workers are commonly exposed by inhalation, ingestion, and dermal routes while actively spraying pesticides or exposure to residues after spraying occurs (Ferland et al., 2015; Panuwet et al., 2008; Thiphom et al., 2014; Wei et al., 2012). Textile manufacturing and forestry management personnel are exposed primarily by contact with pyrethroid-treated fabrics (Lu et al., 2013; Rossbach et al., 2014, 2016).

Within the US and other militaries, permethrin is used in area spraying and in the treatment of bed nets and uniforms to protect personnel against biting insects and insects that are potential disease vectors (Armed Forces Pest Management Board , 2015). In laboratory and field settings, permethrin-treated uniforms have high efficacy against mosquito, tick and sand fly bites (Faulde et al., 2015; Frances et al., 2014; Gopalakirshnan et al., 2014; Khoobdel, 2008). Studies conducted by both the US and German Army have shown that permethrin is absorbed primarily via dermal exposure as a result of wearing the treated uniforms, and biomarkers of permethrin exposure increase as wear-time increases. In the US Army, wear-time scenarios were compared, and results showed that continuously wearing a uniform (30–32 h continuous wear) was associated with permethrin concentrations 2–3 times higher (2.2 times higher for sum of DCCA metabolites and 3.3 times higher for 3-PBA) than wearing a uniform during the workday (8 h/day, 3 days) (Proctor et al., 2014). German Soldiers wearing permethrin-treated uniforms had significantly higher concentrations of permethrin metabolites in their urine compared to Soldiers wearing conventional (untreated) uniforms (Appel et al., 2008; Kegel et al., 2014; Rossbach et al., 2010). Among Soldiers wearing permethrin-treated uniforms, permethrin metabolites were detected in 100% of urine samples and median concentrations significantly increased after 14 and 28 days of wearing a permethrin-treated uniform during regular office hours compared to baseline levels (Rossbach et al., 2010). In a group of deployed German Soldiers, median permethrin metabolite concentrations in urine samples decreased with increasing days of use (0 through > 120 days) and increasing number of launderings which both lead to loss of permethrin from the treated uniforms (Kegel et al., 2014).

In non-occupationally exposed populations, the main source of pyrethroid exposure is through the diet via ingestion of insecticide residue on produce and other crop-based foods, and exposure to pyrethroid residues and contaminated dust after residential spraying (McKelvey et al., 2013; Riederer et al., 2008; Trunnelle et al., 2014). Many countries, including Germany, Japan, Poland, France, England, and Korea have found evidence of pyrethroid exposure in urine samples of the general population (Bevan et al., 2013; Fréry et al., 2010; Heudorf and Angerer, 2001; Thiphom et al., 2014; Ueyama et al., 2009; Wielgomas and Piskunowicz, 2013; Yoo et al., 2016). In reports of large health studies in the US, Canada, and France, pyrethroid exposure has been characterized for the general population (Barr et al., 2010; CDC, 2017; Fréry et al., 2010; Health Canada, 2013). Germany, England, and Canada have used their population-based studies to estimate reference values (RV) (Germany RV: 3-PBA = 2 μg/L, *trans*-DCCA = 2 μg/L, *cis*-DCCA = 1 μg/L; England RV: 3-PBA = 4.3 μg/L, *trans*-DCCA = 1.8 μg/L, *cis*-DCCA = 0.7 μg/L; Canada RV (ages 20–70): 3-PBA = 5.7 μg/L) (Apel et al., 2017; Bevan et al., 2013; Khoury et al., 2018).

Urinary metabolites of pyrethroid insecticides were examined first in the general US population as part of the 2001–2002 National Health and Nutrition Examination Survey (NHANES). In that NHANES sampling, 3-PBA, a biomarker of general pyrethroid exposure, was detected in 75.8% of adult (aged 20–59 years) samples (Barr et al., 2010). Among adults in the NHANES survey, *cis*-DCCA and *trans*-DCCA were detected in fewer samples, 32.6% and 24.7%, respectively (Barr et al., 2010). In Barr et al. (2010), race was significantly associated with 3-PBA concentrations, with higher levels seen in Non-Hispanic blacks compared to non-Hispanic white and Mexican American samples. Other demographic factors, including gender and age group, were not significantly associated with pyrethroid metabolite concentrations.

In the present study we report the group level urinary concentrations of 3-PBA, *cis*-DCCA and *trans*-DCCA measured in two distinct US Army cohorts, (1) Soldier recruits during Basic Combat Training (BCT) and (2) National Guard Soldiers during Annual Training (AT), and compare and contrast biomarker concentrations in these military personnel to the general US population from the 2009–2010 NHANES survey. As part of this review, we summarize these pyrethroid metabolite concentrations reported in previously published biomonitoring studies within other military, occupational, and non-occupational populations.

2. Methods

This study includes data from two separate prospective military cohort studies (Proctor et al., 2018; Scarpaci et al., unpublished results) and publicly available data from NHANES 2009–2010. In addition, a search was performed in PubMed and Google Scholar to find other cohort studies reporting permethrin and/or pyrethroid biomonitoring data. Search terms included, “pyrethroid(s), permethrin, pesticide, insecticide, biomonitoring, biomarker(s), metabolite(s), occupational, exposure, military, treated-uniform, urine, urinary, 3-phenoxybenzoic acid, DCCA, human.” Literature was categorized into occupational, military, and general population studies for the purpose of comparing permethrin metabolite concentrations among these groups. The reference lists of these papers were examined for additional literature or government reports to review. Studies were excluded if they were not published in English. Papers were excluded in their subjects were pregnant women, recruited in a clinical setting, and/or family members of an occupational cohort. For country-specific population papers outside the U.S., the paper or report with the most complete descriptive data for the biomarkers was included for each country. Finally, papers were included in the comparison if creatinine-adjusted biomonitoring data was provided for pyrethroid biomarkers 3-PBA, *cis*- and *trans*-DCCA.

2.1. Military cohort studies

The protocol for the two studies outlined below was reviewed and approved by the US Army Research Institute of Environmental Medicine Institutional Review Board (USARIEM IRB) and the US Army Medical Research and Materiel Command IRB. The investigators adhered to the policies for protection of human subjects as prescribed in Army Regulation 70–25 and the research was conducted in adherence with the provisions of 32 CFR Part 219. All participants gave their informed consent prior to the research study.

2.1.1. Military group 1 study design and participants

In the fall of 2015, Soldier volunteers were recruited to participate in the study from US Army Basic Combat Training (BCT) located in the Midwestern US. Recruitment and enrollment occurred at the beginning of BCT when trainees had just received their first permethrin-treated uniform. Army uniforms are factory-treated using a polymer coating method to apply permethrin (*cis/trans* ratio 35:65) to the blouse and trousers of the uniform. All uniforms must meet Environmental Protection Agency (EPA) and Army standards for the concentration of active ingredient on the fabric (0.095 mg/cm^2 – 0.135 mg/cm^2) and bite protection (USEPA, 2009). Sixty participants were enrolled in the study, and 44 participants remained at the end of the study, with the rest being lost to follow up (attrition rate of 26.7%) either due to leaving military service or deciding to not continue with study participation.

Group 1 data was collected during three multi-day collection periods during 10-week BCT. The first data collection period occurred during the first week of training, with the second collection following four weeks later and the third collection four weeks after that. In total, 21 urine samples were collected from each participant during the BCT period with 15 (five from each of the three data collection sessions) being analyzed for permethrin metabolites. Further details of this study are described in Proctor et al. (2018).

2.1.2. Military group 2 study design and participants

Between 2016 and 2017, Soldier volunteers were recruited from three different US Army National Guard (NG) Annual Training exercises conducted in two New England states during their respective summer AT sessions. These Soldiers differed from BCT recruits in that they had worn and owned permethrin-treated uniforms for longer periods of time and thus, provide a comparison military group where the estimate of permethrin exposure from uniform wear reflects extended uniform wear time. Fifty participants were enrolled and 47 of those participants completed the study (attrition rate of 6%). Data collection occurred over nine consecutive days. A total of 13 urine samples were collected per participant, with ten being analyzed for permethrin biomarkers. This study is described in more detail in Scarpaci et al. (unpublished results).

2.1.3. Urine sample collection

Urine samples were collected following the same procedure in each US Army study. First morning urine voids were collected daily from all participants, typically between 0400 and 0500 within Group 1 and 0600–0700 within Group 2 depending on wakeup time.

The urine was split into aliquots and frozen after being received from the participant to preserve the integrity of the biomarker compounds, and a randomly selected urine sample was duplicated for each participant to verify the accuracy of the analysis. At the end of each trip, the frozen urine samples were shipped overnight in dry ice to the Centers for Disease Control and Prevention (CDC) for analysis. Each urine sample was analyzed using high performance liquid chromatography mass spectrometry (HPLC-MS) for the three relevant permethrin biomarkers (3-PBA, *cis*- and *trans*-DCCA) and urinary creatinine (Davis et al., 2013). The reported limits of detection (LOD) for the analyses of the permethrin biomarkers were 0.1 μg/L for 3-PBA, 0.6 μg/L for *trans*-DCCA, and 0.5 μg/L for *cis*-DCCA. The mean relative percent difference (RPD) for duplicate aliquots fell below 20% (i.e., Study 1: 0.9%, 1.9%, and 3.8% and Study 2: 2.5%, 2.1%, and 13.3% for 3-PBA, *trans*- and *cis*-DCCA, respectively).

2.2. NHANES 2009–2010

2.2.1. Study population

Interview and laboratory data from NHANES 2009–2010 is available for public use through the National Center for Health Statistics (NCHS) of the CDC (CDC, 2009). NHANES is designed to include a representative sample of the general US population. Sampling weights specific to the demographic data file were used to determine the gender and racial make-up of the general US population. At the time of the interview, spot urine samples were collected during a standardized examination and one-third of the urine samples were randomly selected to be analyzed using HPLC-MS for pyrethroid metabolites (μg/L) and creatinine (g/L) (Davis et al., 2013). Data for 3-PBA and *trans*-DCCA were available in NHANES 2009–2010, but *cis*-DCCA concentrations were not available in the public data set. Demographic variables collected during NHANES in-person interviews (age, sex, and race/ethnicity) were obtained along with the urinary permethrin metabolite concentrations. A sampling weight specific to the pyrethroid metabolite data file was used to estimate 3-PBA and *trans*-DCCA biomarker concentrations for the general US population. The reported LOD for the analysis of permethrin biomarkers were 0.1 μg/L for 3-PBA and 0.6 μg/L for *trans*-DCCA.

2.3. Data management

For comparison to US general population levels, within the military studies, biomarker concentrations measured in the final urine sample collected during the study were selected as they likely were the best representation of long-term exposure. Data was available for 44 participants from Group 1 (BCT). For Group 2 (Army NG) 45 participants were included in these analyses; two Soldiers were excluded because they were not wearing permethrin-treated uniforms during the study period. Military groups 1 and 2 were analyzed separately since the exposure period to permethrin-treated uniforms were different. In the 2009–2010 NHANES dataset results below the LOD were given the value of LOD/√2. This method was also applied to results below the LOD in the US military groups. To account for the effect of hydration level on urinary biomarker concentrations, permethrin metabolite concentrations were adjusted for urinary creatinine levels (μg/g creatinine). We included all samples, regardless of creatinine levels, in the analyses of the US military groups and the 2009–2010 NHANES data staying consistent with statistical methods in the Barr et al. (2010) analyses of 1999–2002 NHANES pyrethroid metabolite data. It was common among other cohort studies to restrict based on creatinine levels below 0.3 g/L and above 3.0 g/L because of extremely dilute or concentrated urine samples. However, the descriptive statistics calculated for the analyses (e.g., geometric mean, median) are less influenced by extreme values that may result from including samples with creatinine levels outside this range.

Within each study group the geometric mean, median, and 95th percentiles were calculated for each creatinine-adjusted permethrin metabolite (3-PBA, *trans*-DCCA, and *cis*-DCCA). For the two military groups, 95% confidence intervals were calculated for the 95th percentile to examine the possible influence of extreme values on the 95th percentile due to relatively small sample sizes (Group 1, n = 44; Group 2, n = 45). Separately, the same descriptive statistics were determined for creatinine-adjusted concentrations of 3-PBA and *trans*-DCCA in the general US population from the 2009–2010 NHANES (CDC, 2009). To accurately estimate pyrethroid metabolite levels in the general US population, the sampling weight specific to the pyrethroid metabolite subsample from NHANES 2009–2010 was used to account for the complex survey design and oversampling of certain demographic groups. Descriptive statistics were generated using the entire pyrethroid metabolite subsample, but only results from adults aged 20–59 are shown in this paper. Because the demographic make-up of the two military groups differed from the general US population, particularly sex (male, female) and race (White, Black, Hispanic, and Other) distributions, the geometric means of the military groups were separately standardized by sex and race according to the distributions of these demographic variables in the general US population.

Table 1
Urinary concentrations of pyrethroid metabolites among two military samples and adults in the general US population (NHANES, 2009–2010).

	N	GM	Sex-standardized GM[a]	Race-standardized GM[a]	Median	P95
3-PBA (µg/g creatinine)						
Adult US population[b]	1296	0.419	–	–	0.365	4.72
Military Group 1	44	17.9	18.2	17.9	17.3	39.3
Military Group 2	45	16.9	17.1	16.4	17.4	67.5
***trans*-DCCA (µg/g creatinine)**						
Adult US population[b]	1309	< LOD	–	–	< LOD	4.4
Military Group 1	44	25.5	26.5	25.4	25.4	61.8
Military Group 2	44[c]	17.7	19.2	17.7	23.8	115.6

GM = geometric mean; P95 = 95th percentile.
For all groups, the LODs were 3-PBA = 0.1 µg/L; *trans*-DCCA = 0.6 µg/L.
[a] Sex- and race-standardized to general US population, NHANES 2009–2010.
[b] Adult population, aged 20–59 years.
[c] n = 44 due to interfering substance in sample during laboratory analysis.

3. Results

3.1. Comparison of US military cohorts to US general population

In Military Group 1, the population was 69.5% male and 70.0% White, 6.7% Black, 15.0% Hispanic, and 8.3% Other, with a mean age of 20.8 years (range: 18–29 years). In Military Group 2, the population was 83.0% male and 76.6% White, 4.3% Black, 17.0% Hispanic, and 2.1% Other, with an average age of 27.8 years (range: 20–53 years). In NHANES 2009–2010, sex distribution was 49% male and the racial distributions were – non-Hispanic White (64.6%), non-Hispanic Black (12.1%), Hispanic/Latino (15.9%) and Other (7.39%). The sex- and race-standardized geometric means of the military groups are notably different from the NHANES geometric means (Table 1). However, they do not appear to deviate significantly from the respective non-standardized geometric mean values.

Among adults, aged 20–59, in the US population, the levels of 3-PBA are substantially lower than 3-PBA concentrations measured in both military groups; the 95th percentile concentration is 3–4 times lower than the median values in each military group (Table 1). A similar pattern is seen for *trans*-DCCA concentrations. Similar metabolite concentrations were observed within the two US military groups: Active Duty (AD) recruit Soldiers completing BCT (Group 1) and NG Soldiers completing an Annual Training Exercise (Group 2) (Tables 1 and 2).

3.2. Comparisons to other populations

Table 2 shows comparisons of the US military groups to other military populations wearing permethrin-treated uniforms identified through the literature review. Permethrin biomarkers are detected with high frequency in all military populations (78–100% detection). With the exception of *trans*-DCCA, the 95th percentile concentrations of the metabolites of interest among US Military Groups 1 and 2 are higher than the concentrations reported by the German Army study conducted in Kabul, Afghanistan (Appel et al., 2008). Compared to the US military groups presented, median levels of 3-PBA, *trans*-DCCA, and *cis*-DCCA measured in the German military are moderately lower (Appel et al., 2008; Rossbach et al., 2010). All studies report biomarker concentrations at least an order of magnitude above those found in the 2009–2010 NHANES general US population survey (Table 1).

Creatinine-adjusted biomarker concentrations published in studies examining occupational exposure to pyrethroid insecticides are summarized in Table 3. 3-PBA is the most commonly reported metabolite across the occupational literature. The frequency of 3-PBA detection in urine samples is high across occupational studies (67–100% detection). When comparing the levels of 3-PBA found in the two US military groups studied, we find they have higher geometric mean and median concentrations of creatinine-adjusted 3-PBA compared to the other occupational groups with reported geometric mean and median values.

Table 2
Urinary concentrations of permethrin metabolites in cohort studies of military personnel wearing permethrin-treated uniforms.

	US Military Groups[a]		Appel et al. (2008) [b]Rossbach et al. (2010)	
Sample Location	Midwest, USA	Northeast USA	Kabul, Afghanistan	Germany
Occupation	Military Group 1	Military Group 2	Military Study 1	Military Study 2
Sampling period	Fall 2015	Summer 2016, Summer 2017	November 2003–January 2004	February-April 2005
Sample size	44	45[c]	243	63
Statistical treatment of values below LOD	LOD/√2		LOD/2	
Restriction by creatinine level	None		Restricted to samples between 0.5 and 2.5 g/L creatinine	
3-PBA (µg/g creatinine)				
LOD (µg/L)	0.1	0.1	0.02	0.02
% detect	100%	97.7%	100%	90.0%
GM	17.9	16.9	–	4.1
Median	17.3	17.4	7.93	4.9
P95	39.3	67.5	24.10	–
***trans*-DCCA (µg/g creatinine)**				
LOD (µg/L)	0.6	0.6	0.03	
% detect	100%	90.9%	100%	
GM	25.5	17.7	–	
Median	25.4	23.8	17.81	
P95	61.8	115.6	60.05	
***cis*-DCCA (µg/g creatinine)**				
LOD (µg/L)	0.5	0.5	0.03	
% detect	97.7%	77.8%	100%	
GM	12.0	6.1	–	
Median	10.9	9.7	2.52	
P95	31.8	28.4	7.86	

LOD = limit of detection; GM = geometric mean; P95 = 95th percentile.
[a] US Military Groups: Group 1 (sample taken Week 9 of 10 week BCT); Group 2 (sample taken Day 9 during Army NG training).
[b] Appel et al. (2008) and Rossbach et al. (2010): Study 1 (Soldiers wearing permethrin-treated uniforms during deployment); Study 2 (sample taken after 28 days of wearing treated-uniforms).
[c] n = 44 for trans-DCCA due to interfering substance in the sample during laboratory analysis.

The median concentration of 3-PBA measured in farmers in Thailand was comparable to concentrations measured in the US military groups (Thiphom et al., 2014). Among those studies that reported 95th percentile concentrations for 3-PBA, textile production workers demonstrated the highest reported levels (Lu et al., 2013); these were similar to the 95th percentile concentrations measured among US military

Table 3
Urinary concentrations of pyrethroid metabolites in two US military samples and studies of occupational exposure to pyrethroid insecticides.

	US Military Groups		Arcury et al. (2018)		Hardt and Angerer (2003)		Lu et al. (2013)	Thiphom et al. (2014)	Panuwet et al. (2008)	Wang et al. (2007)	Wei et al. (2012)
Sample Location	Midwest, USA	Northeast USA	North Carolina, USA		Germany		China	Thailand	Thailand	Japan	US
Occupation	Military Group 1	Military Group 2	Farmworkers	Non-farmworkers[c]	Agriculture	Pest control	Textile Production	Farmers	Farmers	Pest control	Flight attendants
Sampling period	Fall 2015	Summer 2016, Summer 2017	May-October 2012		–	–	2010	–	June 2006	August 2005	2009–2010
Sample size	44	45[d]	142	89	19	15	30	100	136	44	11
Statistical treatment of values below LOD	LOD/√2		Values below LOQ not included in analysis		LOD/2		MDL/2	Values below LOD not included	LOD/√2	LOD/2	LOD/√2
Restriction by creatinine level	None		None		Restricted to samples between 0.3 and 2.8 g/L creatinine		None	None	None	None	None
3-PBA (μg/g creatinine)											
LOD (μg/L)	0.1	0.1	0.5[a]	0.5[a]	0.5	0.5	0.1[b]	.0025	0.1	0.04	0.08
% detect	100%	97.7%	69.9%	69.0%	67%	90%	100%	69%	86.8%	95.5%	100%
GM	17.9	16.9	1.04	1.71	–	–	–		0.86	12.2	9.01
Median	17.3	17.4	1.05	1.41	0.6	1.4	4.2	16.1	0.98	–	4.13
P95	39.3	67.5	3.94	20.47	–	–	69		7.4	–	36.27
***trans*-DCCA (μg/g creatinine)**											
LOD (μg/L)	0.6	0.6					0.1[b]		0.2		0.08
% detect	100%	90.9%					100%		37.5%		92%
GM	25.5	17.7					–		–		3.92
Median	25.4	23.8					1.4		< LOD		1.71
P95	61.8	115.6					5.1		11.1		15.78
***cis*-DCCA (μg/g creatinine)**											
LOD (μg/L)	0.5	0.5					0.1[b]		0.4		0.08
% detect	97.7%	77.8%					100%		2.9%		77%
GM	12.0	6.1					–		–		0.98
Median	10.9	9.7					4.3		< LOD		0.46
P95	31.8	28.4					126		< LOD		4.30

LOD = limit of detection; LOQ = limit of quantification; MDL = method detection limit; GM = geometric mean; P95 = 95th percentile.
[a] Limit of quantification.
[b] Method detection limit.
[c] Non-farmworkers held occupations in construction and maintenance, manufacturing, and other job categories.
[d] n = 44 for trans-DCCA due to interfering substance in the sample during laboratory analysis.

Table 4
Urinary concentrations of pyrethroid metabolites in two US military samples and general population studies.

Variable of Interest	US Military Groups		McKelvey et al. (2013)	Trunnelle et al. (2014)	Health Canada, 2013	Bevan et al. (2013)	Fréry et al. (2010)	Heudorf and Angerer (2001)	Wielgomas and Piskunowicz (2013)	Thiphom et al. (2014)	Ueyama et al. (2009)	Yoo et al. (2016)
Sample Location	Midwest, USA	Northeast, USA	New York City, USA	California, USA	Canada	England	France	Frankfurt, Germany	Poland	Fang District, Thailand	Hokkaido, Japan	Korea
Population	Military adults, aged 18-29	Military adults, aged 18-53	Adults, aged 20+	Adults, aged 18-59	Adults, aged 20-39	Adults, 18+	Adults, aged 18-74	Adults, aged 20+	Adults, aged > 18	Adults	Non-farming adults, aged 39-85	Adults, aged 19+
Sampling Period	Fall 2015	Summer 2016, Summer 2017	2004	December 2007–November 2009	2007–2009	–	2006–2007	1998	May–June 2012	–	August 2005	2009–2011
Sample size	44	45[a]	1452	90	1155[b]	336[c]	396	483	190	100	448	3671
Statistical treatment of values below LOD	LOD/√2		LOD/√2	LOD/√2	LOD/2	Excluded	–	None	LOD/√2	Excluded	LOD/2	None
3-PBA (μg/g creatinine)												
LOD (μg/L)	0.1	0.1	0.64	0.58–0.75	0.01	0.5 nM	–		0.1	0.0025	0.02	0.015
Detection Rate	100%	97.7%	58.5%	64%	99.6%	87%	–		–	76%	98%	–
Geometric Mean	17.9	16.9	–	–	0.28	–	0.72		0.138	–	0.29	1.83
Median	17.3	17.4	0.75	0.61	0.23	–	0.63		–	8.86	0.36	–
P95	39.3	67.5	4.51	12.61	2.4	4.3	3.48		–	–	2.33	–
***trans*-DCCA (μg/g creatinine)**												
LOD (μg/L)	0.6	0.6	1.39		0.01	0.5 nM	–	0.2				
Detection Rate	100%	90.9%	14.0%		99.4%	66%	–	61.7%				
Geometric Mean	25.5	17.7	–		0.22	–	0.38	–				
Median	25.4	23.8	< LOD		0.17	–	0.31	0.17				
P95	61.8	115.6	6.66		2.3	1.8	2.64	1.28				
***cis*-DCCA (μg/g creatinine)**												
LOD (μg/L)	0.5	0.5			0.007	0.5 nM	–	0.2				
Detection Rate	97.7%	77.8%			98.8%	54%	55%	28.0%				
Geometric Mean	12.0	6.1			0.096	–	0.16	–				
Median	10.9	9.7			0.084	–	0.14	< LOD				
P95	31.8	28.4			0.82	0.7	1.24	0.53				

[a] n = 44 for trans-DCCA due to interfering substance in the sample during laboratory analysis.
[b] Sample size differed by metabolite: 3-PBA, n = 1155; *trans*-DCCA, n = 1147, *cis*-DCCA, n = 1154.
[c] Sample size within accepted limits for urinary creatinine (between 0.3 and 3.0 g/L); sample size for *trans*-DCCA, n = 335.

Group 2.

Fewer occupational studies reported levels of *trans*- and *cis*-DCCA. Compared to the two US military groups, the median values of both metabolites were lower in textile production workers (Lu et al., 2013), flight attendants (Wei et al., 2012), and farmers (Panuwet et al., 2008). However, the 95th percentile concentration of *cis*-DCCA measured in textile production workers was considerably higher than levels found in the US and German military groups.

Table 4 presents the metabolite concentrations reported from several population studies. Similar to the US military groups, 3-PBA was detected with high frequency in population samples from Canada, England and Japan and concentrations were comparable to the US general population levels (NHANES, 2009–2010) (Table 1). However, the reported geometric mean, median, and 95th percentile concentrations are markedly lower than the US military groups (Table 4). Few population studies reported levels of *trans*- and *cis*-DCCA, but levels were similarly low among the general population in the identified studies compared to the US military groups.

4. Discussion

Since 2013, when Army policy was introduced requiring wear of permethrin-treated uniforms, with exceptions for allergies to the chemical and pregnant and breastfeeding women, an annual population of approximately 471,000 individuals are occupationally exposed on an almost daily basis (USAPHC, 2018). The two US Army cohorts in this study represent a small portion of the total Army population; among this small sample we observed permethrin biomarker concentrations that are markedly higher compared to adults in the US general population using data from the NHANES 2009–2010. This finding indicates that dermal exposure from the wear of permethrin-treated uniforms is a significant source of exposure compared to trace amounts of pyrethroid insecticides the general population are exposed to via diet and contaminated dust. Due to the relatively small sample size of the two military groups, precision of the 95th percentile level was examined and the Group 1 (metabolite 95th percentile (95% CI): 3-PBA = 39.3 (37.9, 44.8), *trans*-DCCA = 61.8 (52.2, 76.5), *cis*-DCCA = 31.8 (27.7, 37.3)) results were found to be more precise than Group 2 (metabolite 95th percentile (95% CI): 3-PBA = 67.5 (57.9, 177.3), *trans*-DCCA = 115.6 (77.3, 132.6), *cis*-DCCA = 28.4 (24.8, 132.3)). This finding is expected because of the differences in the military population between groups. All Soldiers in Group 1 wore new uniforms from the beginning of the study; Soldiers in Group 2 were National Guardsman wearing uniforms that they currently owned at various stages of age and wear. It is likely there was a wider range in the amount of permethrin in the uniforms worn by participants in Group 2 and thus exposure differed between the Groups.

There are few studies reporting biomonitoring data in military personnel wearing permethrin-treated uniforms. Soldiers in Proctor et al. (2014) were asked to wear permethrin-treated uniforms for the first time for 30–32 h consecutively (Study A) or for three work days (8 h/day) (Study B) in a controlled setting. Twelve hours after removing their uniforms, Soldiers in Study B had comparable or lower 95th percentile permethrin concentrations than the military cohorts reported in Table 2 (95th percentile: 3-PBA = 46.3 μg/g creatinine, *trans*-DCCA = 65.0 μg/g creatinine, *cis*-DCCA = 17.2 μg/g creatinine); however, higher metabolite concentrations were measured in Study A (95th percentile: 3-PBA = 99.8 μg/g creatinine, *trans*-DCCA = 203.0 μg/g creatinine, *cis*-DCCA = 84.9 μg/g creatinine). Compared to German Soldiers, higher levels were observed in the US Soldiers and may be explained by differences in wear-time over the study period and/or the permethrin formulation applied to the uniforms. The cohort of German Soldiers stationed in Germany were wearing their uniforms during the work week, while the US Soldiers were in training situations where uniforms were worn almost daily. Additionally, the German Army uses a different permethrin formula (*cis/trans* ratio 25:75) than the formula applied to US Army uniforms (Appel et al., 2008; Rossbach et al., 2010).

Examining reported concentrations of the general pyrethroid biomarker, 3-PBA, in other occupational and population cohorts, we observe a relatively high frequency of detection indicating widespread exposure to pyrethroid insecticides. Frequency of detection in urine samples was between 67 and 100% in occupational cohorts of farmworkers, pest control and textile production workers, and flight attendants. Pyrethroid exposure is seen globally with frequencies of 3-PBA detection ranging from 59 to 100% among general population samples from countries in North America, Europe, and Asia. However, the observed permethrin concentrations in US Soldiers is consistently higher than pyrethroid metabolite levels measured in occupational and general population cohorts. Differences in frequency of detection and biomarker concentrations among these studies are most likely due to differences in the frequency, intensity, and route of exposure, as well as, the specific type of pyrethroid present.

An important difference between the US and German military studies and the rest of the populations reviewed in this paper is the specificity of pyrethroid exposure. In the military groups permethrin is the known pesticide being applied to the uniforms and is therefore the major source of pyrethroid metabolites measured in urine samples. Additionally, in Wei et al. (2012), flight attendants self-reported that permethrin was the insecticide that was being sprayed in the aircrafts. However, studies examining other industries reported the use of other pyrethroid insecticides, in addition to permethrin. In this study, we compare the metabolites (3-PBA, *cis*-DCCA, and *trans*-DCCA) that are often used to characterize permethrin exposure; however, they are not specific to permethrin. While permethrin is the most commonly used pyrethroid world-wide, it is possible that the biomonitoring data from the non-military studies are capturing exposure to pyrethroid insecticides other than permethrin, so the direct comparison of military cohorts to other occupational and population cohorts may not be completely accurate. For example, in Lu et al. (2013), textile workers have noticeably increased levels of *cis*-DCCA compared to military and flight attendants exposed to permethrin, indicating possible exposure to a pyrethroid other than permethrin or to permethrin with a higher proportion of *cis*-to *trans*-isomers compared to the formula applied to US military uniforms (i.e., *cis:trans*-isomer ratio, 35:65).

Other factors that could limit comparability of frequency of detection and metabolite concentrations are differences between studies regarding sample size, LODs, the treatment of samples below the LOD, or exclusion of samples based on creatinine levels. Urine biomarker concentration can be affected by age, sex, race/ethnicity, and body mass index (Barr et al., 2005). Correcting measured metabolite levels for creatinine concentration accounts for variable water content in urine samples and allows for a more accurate comparison between individuals from different demographic groups than uncorrected biomarker concentrations. However, applying this criteria limited our comparisons to studies that published creatinine-corrected biomarker concentrations. Rossbach et al. (2016) analyzed uncorrected permethrin metabolite concentrations in a group of forestry workers wearing permethrin-treated pants during the work week, where the frequency and route of exposure is similar to that of military personnel. After 1 week of wearing permethrin-treated pants, the median concentration of the sum of permethrin metabolites (3-PBA, *cis*- and *trans*-DCCA) was 12.5 μg/L (range: 3.6–38.7 μg/L). These values are notably lower than the uncorrected sum of metabolites measured in military Group 1 (median = 70.3 μg/L, range: 2.1–267.5 μg/L) and Group 2 (median 77.7 μg/L, range: 0.8–462.5 μg/L). This may be due to differences between the groups in terms of occupational activity or uniform characteristics (i.e., forestry workers only wore treated pants for an 8-h period or potential differences in uniform laundering and age). Two occupational studies that were excluded because they described uncorrected metabolite concentrations reported detection rates lower than what was described in studies presented (Table 3). In a study of migrant farmworkers in Eastern North Carolina, 3-PBA was detected in 43% of urine samples, and frequency of detection was between 65 and 74% in groups of low and high exposed forestry workers in the Southern US (Ahn et al., 2011; Raymer et al., 2014). There are other comparisons of uncorrected biomarker concentrations in the literature examining both occupational and population cohorts (Heudorf et al., 2006; Khoury et al., 2018; Saillenfait et al., 2015).

While pyrethroid insecticides are considered to have low toxicity to humans compared to other pesticides, they have been linked to some adverse effects on male reproduction (Jurewicz et al., 2015; Young et al., 2013) and the respiratory system (Hoppin et al., 2008; Ye et al., 2016), as well as associations with some cancers (Alavanja et al., 2014; Rusiecki et al., 2009) and cognitive dysfunction (Furlong et al., 2017; Gunier et al., 2017; Quirós-Alcalá et al., 2014). Continued biomonitoring among occupationally and non-occupationally exposed populations and tracking of potential longer-term health effects are recommended. Comparing biomonitoring data from NHANES over time has demonstrated an increase in permethrin biomarker concentrations in the US adult population. Specifically, the GM of 3-PBA among adults, aged 20–59 in NHANES 2001–2002 was 0.31 μg/g creatinine compared to 0.42 μg/g creatinine in NHANES 2009–2010, and the 95th percentile increased from 2.89 μg/g creatinine to 4.72 μg/g creatinine in those same survey years (Barr et al., 2010; CDC, 2009; CDC, 2017). Similar increases were observed for the 95th percentile of *trans*-DCCA urinary concentrations. However, it is also important to note that permethrin daily dose did not exceed the WHO Acceptable Daily Intake (ADI) for oral ingestion (0.05 mg/kg-d) among the military cohorts presented (Table 2) despite higher metabolite concentrations compared to other populations described (Appel et al., 2008; Proctor et al., 2014; Proctor et al., 2018; Rossbach et al., 2010; Scarpaci et al., unpublished results; WHO, 1999).

5. Conclusion

Biomarkers commonly used to assess exposure to permethrin, and several other pyrethroid insecticides, are found in urine samples across many different occupational groups and general populations in several countries. Sex- and race-standardized concentrations of biomarkers of permethrin exposure were markedly higher in two US military groups compared to the US adult general population. Based on the biomonitoring data reviewed, wearing permethrin-treated uniforms appears to result in higher exposure to permethrin compared to other occupational groups exposed to permethrin and other pyrethroid insecticides.

Declarations of interest

None.

Disclaimer

The opinions or assertions contained herein are the private views of the author(s) and are not to be construed as official or as reflecting the views of the Army or the Department of Defense.

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References

Agency for Toxic Substances and Disease Registry, 2003. Toxicological Profile for Pyrethrins and Pyrethroids. U.S. Department of Health and Human Services, Public Health Service. https://www.atsdr.cdc.gov/toxprofiles/tp155.pdf, Accessed date: 8 October 2018.

Ahn, K.C., Gee, S.J., Kim, H., Aronov, P.A., Vega, H., Krieger, R.I., Hammock, B.D., 2011. Immunochemical analysis of 3-phenoxybenzoic acid, a biomarker of forestry worker exposure to pyrethroid insecticides. Anal. Bioanal. Chem. 401, 1285–1293.

Alavanja, M.C.R., Hofmann, J.N., Lynch, C.F., Hines, C.J., Barry, K.H., Barker, J., Buckman, D.W., Thomas, K., Sandler, D.P., Hoppin, J.A., Koutros, S., Andreotti, G., Lubin, J.H., Blair, A., Beane-Freeman, L.E., 2014. Non-Hodgkin Lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS One 9, e109332. https://doi.org/10.1371/journal.pone.0109322.

Apel, P., Angerer, J., Wilhelm, M., Kolass-Gehring, M., 2017. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int. J. Hyg Environ. Health 220, 152–166.

Appel, K.E., Gundert-Remy, U., Fischer, H., Faulde, M., Mross, K.G., Letzel, S., Rossbach, B., 2008. Risk assessment of Bundeswehr (German Federal Armed Forces) permethrin-impregnated battle dress uniforms (BDU). Int. J. Hyg Environ. Health 211, 88–104.

Arcury, T.A., Chen, H., Laurienti, P.J., Howard, T.D., Barr, D.B., Mora, D.C., Quandt, S.A., 2018. Farmworker and non-farmworker Latino immigrant men in North Carolina have high levels of specific pesticide urinary metabolites. Arch. Environ. Occup. Health 73, 219–227.

Armed Forces Pest Management Board (AFPMB), 2015. Technical Guide No. 36. Personal protective measures against insects and other arthropods of military significance. Armed Forces Pest Management Board, Office of the Assistant Secretary of Defense, Silver Spring, MD.

Barr, D.B., Wilder, L.C., Caudill, S.P., Gonzalez, A.J., Needham, L.L., Pirkle, J.L., 2005. Urinary creatinine concentrations in the US population: implications for urinary biologic monitoring measurements. Environ. Health Perspect. 113, 192–200.

Barr, D.B., Olsson, A.O., Wong, L., Udunka, S., Baker, S.E., Whitehead, R.D., Magsumbol, M.S., Williams, B.L., Needham, L.L., 2010. Urinary concentrations of metabolites of pyrethroid insecticides in the general U.S. population: National Health and Nutrition Examination Survey 1999-2002. Environ. Health Perspect. 118, 742–748.

Bevan, R., Jones, K., Cocker, J., Assem, F.L., Levy, L.S., 2013. Reference ranges for key biomarkers of chemical exposure within the UK population. Int. J. Hyg Environ. Health 216, 170–174.

Centers for Disease Control and Prevention (CDC), 2017. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables. January 2017. vol. 1 accessed 16.02.18. https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2017.pdf.

Centers for Disease Control and Prevention (CDC), 2009. National Center for Health Statistics (NCHS). National Health and Nutrition Examination Survey Data. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, MD. https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2009, Accessed date: 16 February 2018.

Davis, M.D., Wade, E.L., Restrepo, P.R., Roman-Esteva, W., Bravo, R., Kuklenyik, P., Calafat, A.M., 2013. Semi-automated solid phase extraction method for the mass spectrometric quantification of 12 specific metabolites of organophosphorus pesticides, synthetic pyrethroids, and select herbicides in human urine. J Chromatogr. B Analyt. Technol. Biomed. Life Sci. 929, 18–26.

Faulde, M.K., Rutenfranz, M., Keth, A., Hepke, J., Rogge, M., Görner, A., 2015. Pilot study assessing the effectiveness of factory-treated, long-lasting permethrin-impregnated clothing for the prevention of tick bites during occupational tick exposure in highly infested military training areas, Germany. Parasitol. Res. 114, 671–678.

Ferland, S., Côté, J., Ratelle, M., Thuot, R., Bouchard, M., 2015. Detailed urinary excretion time courses of biomarkers of exposure to permethrin and estimated exposure in workers of a corn production farm in Quebec, Canada. Ann. Occup. Hyg. 59, 1152–1167.

Frances, S.P., Sferopoulos, R., Lee, B., 2014. Protection from mosquito biting provided by permethrin-treated military fabrics. J. Med. Entomol. 51, 1220–1226.

Fréry, N., Saoudi, A., Zeghnoun, A., Falq, G., Guldner, L., 2010. Exposure of the French Population to Environmental Pollutants – Environmental Components of the French National Survey on Nutrition and Health – Initial Results. September. Saint-Maurice (Fra): French Institute for Public Health Surveillance, pp. 12. accessed 30.09.2018. www.invs.sante.fr.

Furlong, M.A., Barr, D.B., Wolff, M.S., Engel, S.M., 2017. Prenatal exposure to pyrethroid pesticides and childhood behavior and executive functioning. Neurotoxicology 62, 231–238.

Gopalakirshnan, R., Chaurasia, A.K., Baruah, I., Veer, V., 2014. Evaluation of permethrin-impregnated military uniforms for contact toxicity against mosquitoes and persistence in repeated washings. Int. J. Environ. Sci. Technol. 11, 1855–1860.

Gunier, R.B., Bradman, A., Harley, K.G., Kogut, K., Eskenazi, B., 2017. Prenatal residential proximity to agricultural pesticide use and IQ in 7-year-old children. Environ. Health Perspect. 125, 057002. https://doi.org/10.1289/EHP504.

Hardt, J., Angerer, J., 2003. Biological monitoring of workers after the application of insecticidal pyrethroids. Int. Arch. Occup. Environ. Health 76, 492–498.

Health Canada, 2013. Second Report on Human Biomonitoring of Environmental Chemicals in Canada: Results of the Canadian Health Measures Survey Cycle 2 (2009-2011). Minister of Health, Ottawa, ON accessed 16.02.18. https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/ewh-semt/alt_formats/pdf/pubs/contaminants/chms-ecms-cycle2/chms-ecms-cycle2-eng.pdf.

Heudorf, U., Angerer, J., 2001. Metabolites of pyrethroid insecticides in urine specimens: current exposure in an urban population in Germany. Environ. Health Perspect. 109, 213–217.

Heudorf, U., Butte, W., Schulz, C., Angerer, J., 2006. Reference values for metabolites of pyrethroid and organophosphorous insecticides in urine for human biomonitoring in

environmental medicine. Int. J. Hyg Environ. Health 209, 293–299.
Hoppin, J.A., Umbach, D.M., London, S.J., Henneberger, P.K., Kullman, G.J., Alavanja, M.C.R., Sandler, D.P., 2008. Pesticides and atopic and nonatopic asthma among farm women in the Agricultural Health Study. Am. J. Respir. Crit. Care Med. 177, 11–18.
Jurewicz, J., Radwan, M., Wielgomas, B., Sobala, W., Piskunowicz, M., Radwan, P., Bochenek, M., Hanke, W., 2015. The effect of environmental exposure to pyrethroids and DNA damage in human sperm. Syst. Biol. Reprod. Med. 61, 37–43.
Kegel, P., Letzel, S., Rossbach, B., 2014. Biomonitoring in wearers of permethrin impregnated battle dress uniforms in Afghanistan and Germany. Occup. Environ. Med. 71, 112–117.
Khoobdel, M., 2008. Evaluation of permethrin treated clothing for personal protection against *Phlebotomus papatasi* (Diptera: Psaychodidae). J. Entomol. 5, 51–55.
Khoury, C., Werry, K., Haines, D., Walker, M., Malowany, M., 2018. Human biomonitoring reference values for some non-persistent chemicals in blood and urine derived from the Canadian Health Measures Survey 2009-2013. Int. J. Hyg Environ. Health 221, 684–696.
Lu, D., Wang, D., Feng, C., Jin, Y., Wu, C., Lin, Y., Wang, G., 2013. Urinary concentrations of metabolites of pyrethroid insecticides in textile workers, Eastern China. Environ. Int. 60, 137–144.
McKelvey, W., Jacobson, J.B., Kass, D., Barr, D.B., Davis, M., Calafat, A.M., Aldous, K.M., 2013. Population-based biomonitoring of exposure to organophosphate and pyrethroid pesticides in New York city. Environ. Health Perspect. 121, 1349–1356.
Panuwet, P., Prapamontol, T., Chantara, S., Thavornyuthikarn, P., Montesano, M.A., Whitehead, R.D., Barr, D.B., 2008. Concentrations of urinary pesticide metabolites in small-scale farmers in Chiang Mai Province, Thailand. Sci. Total Environ. 407, 655–668.
Proctor, S.P., Maule, A.L., Heaton, K.J., Adam, G.E., 2014. Permethrin exposure from fabric-treated military uniforms under different wear-time scenarios. J. Expo. Sci. Environ. Epidemiol. 24, 572–578.
Proctor, S.P., Scarpaci, M.M., Maule, A.L., Heaton, K.J., Taylor, K., Haven, C., Rood, J., Ospina, M., Calafat, A., 2018. Role of body composition and physical activity on permethrin urinary biomarker levels while wearing treated military uniforms. Toxicol. Lett. 299, 210–217.
Quirós-Alcalá, L., Mehta, S., Eskenazi, B., 2014. Pyrethroid pesticide exposure and parental report of learning disability and attention deficit/hyperactivity disorder in US Children: NHANES 1999-2002. Environ. Health Perspect. 122, 1336–1342.
Raymer, J.H., Studabaker, W., Gardner, M., Talton, J., Quandt, S.A., Chen, H., Michael, L.C., McCombs, M., Arucry, T.A., 2014. Pesticide exposures to migrant farmworkers in Eastern NC: detection of metabolites in farmworker urine associated with housing violations and camp characteristics. Am. J. Ind. Med. 57, 323–337.
Riederer, A.M., Bartell, S.M., Barr, D.B., Ryan, P.B., 2008. Diet and nondiet predictors of urinary 3-phenoxybenzoic acid in NHANES 1999-2002. Environ. Health Prespect. 116, 1015–1022.
Rossbach, B., Appel, K.E., Mross, K.G., Letzel, S., 2010. Uptake of permethrin from impregnated clothing. Toxicol. Lett. 192, 50–55.
Rossbach, B., Niemietz, A., Kegel, P., Letzel, S., 2014. Uptake and elimination of permethrin related to the use of permethrin treated clothing for forestry workers. Toxicol. Lett. 231, 147–153.
Rossbach, B., Kegel, P., Süß, H., Letzel, S., 2016. Biomonitoring and evaluation of permethrin uptake in forestry workers using permethrin-treated tick-proof pants. J. Expo. Sci. Epidemiol. 26, 95–103.
Rusiecki, J.A., Patel, R., Koutros, S., Beane-Freeman, L., Landgren, O., Bonner, M.R., Coble, J., Lubin, J., Blair, A., Hoppin, J.A., Alavanja, M.C.R., 2009. Cancer incidence among pesticide applicators exposed to permethrin in the agricultural health study. Environ. Health Perspect. 117, 581–586.
Saillenfait, A., Ndiaye, D., Sabaté, J., 2015. Pyrethroids: exposure and health effects – an update. Int. J. Hyg Environ. Health 218, 281–292.
Scarpaci, M.M., Taylor, K., Maule, A.L., Heaton, K.J., Dillon, C., Rood, J., Ospina, M., Calafat, A., Proctor, S.P. The effect of body composition and energy expenditure on body permethrin levels among US Army National Guardsmen. Unpublished results; manuscript currently under review at journal.
Thiphom, S., Prapamontol, T., Chantara, S., Mangklabruks, A., Suphavilai, C., Ahn, K.C., Gee, S.J., Hammock, B.D., 2014. Determination of the pyrethroid insecticide metabolite 3-PBA in plasma and urine samples from farmer and consumer groups in northern Thailand. J. Environ. Sci. Health B. 49, 15–22.
Trunnelle, K.J., Bennett, D.H., Tulve, N.S., Clifton, M.S., Davis, M.D., Calafat, A.M., Moran, R., Tancredi, D.J., Hertz-Picciotto, I., 2014. Urinary pyrethroid and chlorpyrifos metabolite concentrations in Northern California families and their relationship to indoor residential insecticide levels, part of the Study of Use of Products and Exposure Related Behavior (SUPERB). Environ. Sci. Technol. 48, 1931–1939.
Ueyama, J., Kimata, A., Kamijima, M., Hamajima, N., Ito, Y., Suzuki, K., Inoue, T., Yamamoto, K., Takagi, K., Saito, I., Miyamoto, K., Hasegawa, T., Kondo, T., 2009. Urinary excretion of 3-phenoxybenzoic acid in middle-age and elderly general population of Japan. Environ. Res. 109, 175–180.
United States Army Public Health Center (USAPHC), 2018. 2017 health of the force report. accessed 27.03.18. https://phc.amedd.army.mil/Periodical%20Library/2017HealthoftheForceweb.pdf.
United States Environmental Protection Agency (USEPA), 2009. Reregistration Eligibility Decision (RED) for Permethrin. accessed 16.02.18. https://archive.epa.gov/pesticides/reregistration/web/pdf/permethrin-red-revised-may2009.pdf.
Wang, D., Kamijima, M., Imai, R., Suzuki, T., Kameda, Y., Asai, K., Okamura, A., Naito, H., Ueyama, J., Saito, I., Nakajima, T., Goto, M., Shibata, E., Konda, T., Takagi, K., Takagi, K., Wakusawa, S., 2007. Biological monitoring of pyrethroid exposure of pest control workers in Japan. J. Occup. Health 49, 509–514.
Wei, B., Mohan, K.R., Weisel, C.P., 2012. Exposure of flight attendants to pyrethroid insecticides on commercial flights: urinary metabolite levels and implications 215. pp. 465–473.
Wielgomas, B., Piskunowicz, M., 2013. Biomonitoring of pyrethroid exposure among rural and urban populations in northern Poland. Chemosphere 93, 2547–2553.
World Health Organization (WHO), 1999. Toxicological Evaluations: Permethrin. Joint Meeting of the FAO Panel of Experts on Pesticide Residues (JMPR). http://www.inchem.org/documents/jmpr/jmpmono/v99pr07.htm, Accessed date: 16 October 2018.
Ye, M., Beach, J., Martin, J.W., Senthilselvan, A., 2016. Urinary concentrations of pyrethroid metabolites and its association with lung function in a Canadian general population. Occup. Environ. Med. 73 199-126.
Yoo, M., Lim, Y., Kim, T., Lee, D., Hong, Y., 2016. Association between urinary 3-phenoxybenzoic acid and body mass index in Korean adults: 1st Korean National Environmental Health Survey. Ann. Occup. Environ. Med. 28, 2. https://doi.org/10.1186/s40557-015-0079-7. eCollection 2016.
Young, H.A., Meeker, J.D., Martenies, S.E., Figueroa, Z.I., Barr, D.B., Perry, M.J., 2013. Environmental exposure to pyrethroids and sperm sex chromosome dismony: a cross-sectional study. Environ. Health 12, 111.