Comparative Evaluation of Chlorpyrifos Exposure Estimates from Whole-body Dermal Dosimetry and Urinary Trichloro-2-pyridinol (TCP) Methods

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Abstract

Chlorpyrifos is one of the most widely used organophosphate pesticides and has a record of adverse effects on applicators. Assessment of exposure to chlorpyrifos based on its urinary metabolite, 3,5,6-trichloro-2-pyridinol (TCP), is considered as the most accurate. However, urine sampling can be difficult, and the laboratory analytical procedures involved are complex and expensive. A simpler approach for assessing pesticide exposure among applicators is the whole-body dermal dosimetry method, but this needs validation. The objective of this study was to compare chlorpyrifos exposure estimates obtained separately with the urinary TCP and the whole-body dermal dosimetry methods from applicators. Exposure estimates from the whole-body dermal dosimetry method (5 to 29 µg/kg/day) showed less variation than those from the urinary TCP method (1 to 71 µg/kg/day), but both were in close agreement at the mean level (16 µg/kg/day and 15 µg/kg/day, respectively). The whole-body dermal dosimetry method is therefore valid for providing estimates of the typical levels of pesticide exposure among applicators in situations where the urinary TCP method cannot be applied.

1.0 Introduction

Chlorpyrifos is an important organophosphate pesticide used extensively throughout the world that has been associated with adverse health effects among applicators (Garabrant *et al.*, 2009; Farahat *et al.*, 2011; Khan *et al.*, 2014). Exposure to chlorpyrifos among applicators has usually been assessed based on the metabolite, 3,5,6-trichloro-2-pyridinol (TCP) found in the urine of exposed persons (Saieva *et al.*, 2004; Baker *et al.*, 2005; Phung *et al.*, 2012b; Atabila *et al.*, 2018b). The use of urinary TCP for evaluating chlorpyrifos exposure is widely accepted because the method gives a measure of the actual absorbed dose due to exposure (Albertini *et al.*, 2006; Ellison *et al.*, 2012; Fustinoni *et al.*, 2014). The method also takes into account exposures from all routes and therefore presents an overall measure of exposure (Sexton *et al.*, 2004; Albertini *et al.*, 2006; Barr and Angerer, 2006). However, urine sampling can be difficult for some individuals and the laboratory analysis procedures involved are often complex and expensive (Fenske and Day, 2005; Putnam and Clark, 2007; Scher *et al.*, 2007).

The dermal route is the most important pathway by which pesticide applicators are exposed with the back-pack spraying method of application (Dowling and Seiber, 2002; Damalas and Eleftherohorinos, 2011; Fenske *et al.*, 2012). This route may account for about 94-96% of exposure in occupational settings (Fenske *et al.*, 2012). The whole-body dermal dosimetry method of evaluating chlorpyrifos exposure (An *et al.*, 2014; Atabila *et al.*, 2017) may therefore be employed in many situations as an alternative to the urinary TCP method. The whole-body dermal dosimetry method involves the use of absorbent coveralls, hand gloves, socks and skin wipes to intercept pesticide residues that would potentially reach and/or penetrate the skin of applicators during spraying events. Studies have been carried to assess the accuracy of the whole-body dermal dosimetry method with chlorpyrifos among pesticide workers (Geer *et al.*,

2004; Fenske and Day, 2005; Ross *et al.*, 2008). In these studies, whole-body dermal dosimetry and urinary TCP methods were carried out concurrently for each worker for the same exposure event, and the resulting absorbed dose estimates were compared. While these studies provide useful information on how the absorbed dose estimates of chlorpyrifos from the whole-body dermal dosimetry and urinary TCP methods compare with one another, the study designs applied result in the dose estimates for each of the two methods being incomplete. For instance, with the dose estimate from the urinary TCP method, the concurrent dermal dosimeter method results in interception of some quantity of insecticides that would have entered the body of the workers and subsequently eliminated as urinary TCP. This situation can make comparison of the estimated absorbed dose from the two methods problematic. Ideally, each of the two methods should be applied separately and for separate exposure events for comparison of the resulting dose estimates.

We have previously assessed the levels of exposure to chlorpyrifos with rice farmers in Ghana, using the whole-body dermal dosimetry and urinary TCP methods (Atabila *et al.*, 2017; Atabila *et al.*, 2018a; Atabila *et al.*, 2018b). With each applicator, the whole-body dermal dosimetry and urinary TCP methods were carried out separately to evaluate similar exposure events. Thus, the level of chlorpyrifos exposure during each event was fully assessed with either the whole-body dermal dosimetry method or the urinary TCP method, in contrast to previous studies (Geer *et al.*, 2004; Fenske and Day, 2005; Ross *et al.*, 2008), as outlined above. The objective of the present study was to carry out a comparative evaluation of chlorpyrifos exposure estimates from the whole-body dermal dosimetry and urinary TCP methods utilizing the results obtained in the previous investigations (Atabila *et al.*, 2017; Atabila *et al.*, 2018a; Atabila *et al.*, 2018b).

2.0 Methods

The details of the study setting, participants, data collection procedures, laboratory analytical procedures, absorbed dose estimation have been previously described (Atabila *et al.*, 2017; Atabila *et al.*, 2018a; Atabila *et al.*, 2018b). Ethical clearance for the study was obtained from both Ghana Health Service Ethical Review Committee (GHS-ERC: 10/07/15) and Griffith University Human Ethics Committee (ENV/24/15/HREC).

2.1 Study Setting and Participants

The study was conducted among small scale (< 2 ha) rice farmers from a rural farming community located at south-eastern part of Ghana. Chlorpyrifos (480g/L Emulsifiable Concentrate – 480 EC) is regularly applied by the farmers, with the use of hand-pressurized knapsack spraying devices carried on the back. The spraying activities in this study were all carried out in the morning between the hours of 6 to 8 am, when the temperature was generally cooler, and the wind was calm.

2.2 Whole-body Dermal Dosimetry Method

2.2.1 Sampling Procedure

The whole-body dermal dosimetry method carried out in this study was for one chlorpyrifos spray event for each applicator. The method was based on the whole-body dermal dosimetry protocol of the World Health Organisation (1982) and the Organisation for Economic Co-operation and Development (OECD, 1997). During the day of spraying, the applicators were initially dressed in a new set of sampling suit which consisted of Tyvek under-wear garment, white cotton hand gloves and socks. The applicators subsequently wore their usual farm clothes

over the sampling suit before starting pesticide spraying activities. The farm clothes of the applicators mainly consisted of cotton-made short-sleeve shirts and long pants. Only two of the applicators used Personal Protective Equipment (PPE), which was safety glasses. After the spraying event, the sampling suit of each applicator was immediately removed, packed and transported in a sample container with ice to the Pesticides Residues Laboratory of Ghana Standards Authority for analysis (Atabila *et al.*, 2017; Atabila *et al.*, 2018a).

2.2.2 Laboratory Analytical Procedure

The extraction and laboratory analysis of the sampling suit for chlorpyrifos were performed with a modified version of the agricultural chemicals analytical procedures of the Department of Food Safety of Japan (DFS, 2006). A Varian CP 3800 Gas Chromatograph (Varian Associates Inc, USA) equipped with Pulsed Flame Photometric Detector (PFPD) and a CombiPAL auto sampler was used to analyse the extract obtained from the sampling suits (Atabila *et al.*, 2017; Atabila *et al.*, 2018a).

2.2.3 Chlorpyrifos Absorbed Daily Dose Estimation

The Absorbed Daily Dose (ADD_{DEM}) of chlorpyrifos from dermal exposure for each applicator was estimated using the following equation, adapted from Health Canada (2014):

$$\text{ADD}_{\text{DEM}} (\mu\text{g/kg/day}) = (\text{TDE} \times \text{DAF})/\text{BW} \quad \text{Equation 1}$$

where, TDE is Total Dermal Exposure ($\mu\text{g}/\text{day}$), obtained as the total mass of chlorpyrifos residues extracted from the sampling suit for each applicator for a day's spray event; DAF, Dermal Absorption Factor (4.3 %) (Meuling *et al.*, 2005); and BW, Body Weight of each applicator (kg). A rationale for using a DAF of 4.3% is provided in Atabila *et al.* (2018a).

2.3 Urinary TCP Method

2.3.1 Sampling Procedure

Similar to the whole-body dermal dosimetry method, the urinary TCP method was carried out for one chlorpyrifos spray event for each applicator. Prior to each sampling day, each applicator was provided with a set of sampling items, that consisted of an ice chest (8 L), ice packs and a plastic jar (2 L). Each applicator provided six 24-hour (or whole day) urine samples over a period of six days (one sample per day). These included one sample before the application day (background sample), one sample during the application day and four samples after the application day (post-application samples). Three aliquots were prepared from each sample and stored in High-density Polyethylene (HDPE) bottles (60 mL) for laboratory analysis (Atabila *et al.*, 2018b).

2.3.2 Laboratory Analytical Procedure

Aliquots of the urine (1 mL) were spiked with isotopically labelled TCP, treated with 10M NaOH ($\text{pH} > 12$) and hydrolysed at 60°C for two hours. The samples were then adjusted to $\text{pH} < 3$ with 42.5% w/w H_3PO_4 and $0.45\ \mu\text{m}$ filtered. The prepared samples were subsequently analysed using Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) in positive ESI mode on a Shimadzu Prominence UFLC (Kyoto, Japan), coupled to an Applied Biosystems API 4000 mass spectrometer (Framingham, USA) with a Kinetex C18 column ($50 \times 2.1\text{mm}$,

5 μ m, Phenomenex, Torrance, USA) and a 1% to 95% methanol gradient with 0.1% acetic acid.

The analytical quality control consisted of duplicate samples, spiked samples, conjugate spiked samples, blank samples, spiked blank samples and conjugate spiked blank samples (Atabila *et al.*, 2018b).

To compensate for urine volume excretion variation with the applicators, urinary creatinine concentrations were determined and applied to normalize the urinary TCP concentrations of the applicators (Barr *et al.*, 2005; Cocker *et al.*, 2011). The creatinine concentrations were determined based on the kinetic Jaffe reaction colorimetric method (Mohabbati-Kalejahi *et al.*, 2012), with the use of a Mindray BS-120 automated analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd). The analytical quality control consisted of duplicate sample analysis (Atabila *et al.*, 2018b).

2.3.3 Chlorpyrifos Absorbed Daily Dose Estimation

Using the post-application urinary TCP levels, the levels of Absorbed Daily Dose of chlorpyrifos from application exposure (ADD_{TCP}) were calculated from the equation below (Fenske *et al.*, 2012; Phung *et al.*, 2012b):

$$\text{ADD}_{\text{TCP}} (\mu\text{g/kg/day}) = [C \times C_n \times CF \times (\text{MW}_{\text{CPF}}/\text{MW}_{\text{TCP}})]/\text{BW} \quad \text{Equation 2}$$

where, C is the concentration of urinary TCP excreted per day ($\mu\text{g/g}$ creatinine); C_n, expected mass of creatinine excreted per day(g/day); CF, correction factor of 100/70 for urinary TCP (about 70% of chlorpyrifos is excreted as TCP in urine) (Nolan *et al.*, 1984); MW_{CPF}, the

molecular weight of chlorpyrifos (350.6g/mol); MW_{TCP} , the molecular weight of TCP (198.5g/mol); and BW, the body weight of each applicator (kg).

2.4 Data Analysis

In all, 24 applicators participated in the whole-body dermal dosimetry method, whereas 21 applicators participated in the urinary TCP method. However, sixteen of the applicators were involved in both methods. Only the results of this group were analysed in the current study.

2.4.1 *Test of Difference in Field Factors and Chlorpyrifos Exposure Estimates between the Whole-body Dermal Dosimetry and Urinary TCP Methods*

Since the whole-body dermal dosimetry and urinary TCP methods were undertaken during separate exposure events, differences in the field factors between the events could impact on the exposure dose estimates. To investigate this, the non-parametric Wilcoxon signed ranks test was employed to test for differences in medians of non-normally distributed continuous variables (quantity of insecticide applied, farm size and crop height) between the two methods. A normally distributed continuous variable (spraying duration), on the other hand, was investigated using the parametric paired samples t-test on the means. For categorical variables (use of PPE, type of shirt, type of trouser, occurrences of leaky spray tank and insecticide spillage), the non-parametric McNemar test was used to test for differences in proportions. Also, the difference in the means of the exposure estimates between the whole-body dermal dosimetry and urinary TCP methods were evaluated with Wilcoxon signed ranks test. The analysis was performed using the Statistical Package for the Social Sciences (SPSS) program (Version 20).

2.4.2 Cumulative Probability Distribution Plots of Chlorpyrifos Exposure Estimates from the Whole-body Dermal Dosimetry and Urinary TCP Methods

The distributions of the exposure estimates from the whole-body dermal dosimetry and urinary TCP methods were assessed with Cumulative Probability Distribution (CPD) plots. The data of the exposure estimates were ranked from the lowest to the highest. The Cumulative Probability (CP) of each data point was then calculated using the equation below:

$$CP (\%) = (i/n+1) \times 100 \quad \text{Equation 3}$$

where, CP is cumulative probability (%), i , the i^{th} data point and n , the total number of data points.

Using the data points and the CP values, the CPD of the exposure estimates were subsequently plotted.

3.0 Results and Discussion

3.1 Comparison of the Field Factors of the Whole-body Dermal Dosimetry and Urinary TCP Methods

Comparison of the field factors evaluated during both the whole-body dermal dosimetry and urinary TCP methods comprises a validation that the exposure estimates of the two methods can be directly compared. The field factors recorded during the dermal and urinary TCP methods are shown in Table 1. Also shown are the p-values of the statistical tests carried out to investigate differences in the field factors between the two exposure methods. Out of the

nine field factors investigated, only two factors (farm size and spraying duration) differed significantly between the whole-body dermal dosimetry and urinary TCP methods (0.4 ha and 0.6 ha; 53 min and 79 min, respectively; $p < 0.05$). It may therefore be assumed that the field factors of the dermal and biomonitoring methods were similar, especially, when the quantities of insecticide formulation applied during the two methods were not statistically different (156 mL and 162 mL, respectively; $p > 0.05$). Compared to other field factors, quantity of pesticide applied has consistently been identified as a significant determinant of exposure among applicators (Aponso, 2002; Marquart *et al.*, 2003; Bakke *et al.*, 2009; Hines *et al.*, 2011; Phung *et al.*, 2012a; Atabila *et al.*, 2017). Thus, it may be concluded that a direct comparison of the exposure estimates of chlorpyrifos from the whole-body dermal dosimetry method and the urinary TCP method is valid.

Table 1: Field Factors and p-values for Test of Difference in Variables between the Whole-body Dermal Dosimetry and Urinary TCP Methods (n=16).

Field Factor	Whole-body Dermal Dosimetry Method	Urinary TCP Method	p-value
Quantity of Insecticide Formulation Applied (median, mL)	156	162	0.43a
Farm Size (median, ha)	0.4	0.6	0.04a
Crop Height (median, cm)	43	38	0.5a
Spraying Duration (mean, min)	53	79	0.04b
Used PPE (%)	6	13	1c
Wore Short Sleeve Shirt (%)	63	50	0.7c
Wore long trousers (%)	100	94	1c
Occurrence of Leaky Spray Tank (%)	50	50	1c
Occurrence of Spillage (%)	81	81	1c

a, Wilcoxon signed ranks test;
b, paired samples t-test;
c, McNemar test

3.2 Absorbed Daily Dose of Chlorpyrifos Estimated from the Whole-body Dermal Dosimetry Method (ADD_{DEM}) and Urinary TCP Method (ADD_{TCP})

Table 2 shows the descriptive statistics of the Absorbed Daily Dose (ADD) estimates of chlorpyrifos from the whole-body dermal dosimetry method (ADD_{DEM}) and the urinary TCP method (ADD_{TCP}) for the applicators. ADD_{DEM} ranged from 5 to 29 µg/kg/day, with a median and a mean of 16 µg/kg/day. For ADD_{TCP}, the dose estimate ranged from 1 to 71 µg/kg/day, with a median of 5 µg/kg/day and mean of 15 µg/kg/day. Although the median ADD_{DEM} (16 µg/kg/day) was higher than that for ADD_{TCP} (5 µg/kg/day), the difference was not statistically significant ($p > 0.05$). In addition, the means of ADD_{DEM} (16 µg/kg/day) and ADD_{TCP} (15 µg/kg/day) were similar. These suggest that, overall, the two methods yielded comparable results in terms of the central tendency measures. The similarity of the two estimates further show that pesticide exposure through the dermal route can be regarded as the most significant in agricultural settings, considering that urinary TCP method incorporates exposure from other routes, such as via inhalation and oral routes.

Table 2: Absorbed Daily Dose of Chlorpyrifos Estimated from Whole-body Dermal Dosimetry (ADD_{DEM}) and Urinary TCP (ADD_{TCP}) Methods for Applicators.

	Minimum	Median	Mean	Maximum	p-value
ADD _{DEM} (µg/kg/day)	5	16	16	29	0.3a
ADD _{TCP} (µg/kg/day)	1	5	15	71	

a, Wilcoxon signed ranks test of difference of the median values

The CPD plots of ADD_{DEM} and ADD_{TCP} for the individual applicators are shown in Figure 1. The linear regression line of the plot for ADD_{DEM} and ADD_{TCP} are respectively represented by the following equations:

$$CP\% = 55\log(ADD_{DEM}) - 98 \quad (R^2 = 0.91) \quad \text{Equation 4}$$

$$CP\% = 20\log(ADD_{TCP}) + 14 \quad (R^2 = 0.96) \quad \text{Equation 5}$$

The slope of the linear regression line of the plot for ADD_{TCP} was less steep (20) compared to that of the plot for ADD_{DEM} (55). These trends reflect the wide range (1 to 71 µg/kg/day) of ADD_{TCP} values and the short range (5 to 29 µg/kg/day) of ADD_{DEM} values (Table 2).

Figure 1 shows that ADD_{DEM} values were generally higher than those for ADD_{TCP} below the 75th percentile. Conversely, ADD_{DEM} values were less than those for ADD_{TCP} above the 75th percentile. If the exposure dose estimate from the urinary TCP method is accepted as the more valid then, these findings suggest that the whole-body dermal dosimetry method may over-estimate exposure dose at lower percentiles and under-estimate the dose at higher percentiles.

To further investigate the differences trend observed in Figure 1, within the individual applicators, Absorbed Unit Exposure (AUE, %) values of both the whole-body dermal dosimetry and urinary TCP methods for each applicator were calculated and compared. Based on the assumption that pesticide exposure is proportional to the quantity of active ingredient applied (Sielken Jr, 2005; Beauvais *et al.*, 2007; Hines *et al.*, 2011; Phung *et al.*, 2012b; Atabila *et al.*, 2017), AUE values were calculated as a ratio of the mass of estimated absorbed chlorpyrifos to the mass of chlorpyrifos applied, multiplied by 100 to give AUE as a percentage

(AUE %). Thus, high absorbed chlorpyrifos corresponds to high AUE value. Plots of the AUE values are shown in Figure 2. With valid estimate of absorbed chlorpyrifos with the whole-body dermal dosimetry method, the resulting AUE values (AUE_{DEM}) and those from the urinary TCP method (AUE_{TCP}) for each applicator can be expected to be similar. However, Figure 2 shows that AUE_{DEM} values were higher than AUE_{TCP} for applicators A to L (“low exposure” group), reflecting Figure 1 with exposure values below the 75th percentile. On the contrary, the reverse of this trend was true for applicators N to P (“high exposure” group), reflecting Figure 1 with exposure values above the 75th percentile.

The above findings also suggest that the whole-body dermal dosimetry was less able to account for variabilities in absorbed doses between applicators. This is mainly because the method assumes that a fixed fraction (4.3%) of the quantity of insecticide reaching the skin of applicators are absorbed, as demonstrated in the study by Meuling *et al.* (2005). On the other hand, the urinary TCP method could account for variations in exposure doses between the applicators, which can largely be attributed to differences in the dermal absorption fractions between applicators. Dermal absorption fractions are in turn influenced by differences in the quantity of pesticide exposure on the skin, anatomical site of exposure, skin integrity, skin hydration, age and metabolic rates of applicators (Holmgaard and Nielsen, 2009.).

4.0 Conclusions

Overall, the whole-body dermal dosimetry and urinary TCP methods for estimating chlorpyrifos exposure produced similar estimates, based on the means. However, exposure estimates from the urinary TCP method showed more variation than those from the whole-body dermal dosimetry method. Using the exposure estimates from the urinary TCP method as a comparison, the whole-body dermal dosimetry method appeared to over-estimate exposure doses below the 75th percentile and under-estimate the doses above the 75th percentile.

Nevertheless, the whole-body dermal dosimetry method is valid for providing information regarding the typical levels of pesticide exposure among applicators. The urinary TCP method, which can be difficult at applicator and technical levels, may be used to identify the specific variations in exposure of individuals in a population. Moreover, the whole-body dermal dosimetry method may be used to identify the patterns of pesticide exposure on the anatomical regions of applicators.

Conflict of Interest

None

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