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Determinants of Chlorpyrifos Exposures and Urinary 3,5,6-Trichloro-2-Pyridinol Levels Among Termiticide Applicators

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The exposures and work activities of 41 applicators in North Carolina using chlorpyrifos-containing termiticides were characterized. Personal air and urine samples were collected on multiple days within one week. Detailed information about chemical use, tasks, personal protective equipment and hygiene was recorded. During the 202 applicator-days monitored, 415 treatment jobs were performed. Full-shift chlorpyrifos exposures ranged from <0.048 to 110 μg/m³ (*N*=184), with a geometric mean (GM) of 10 μg/m³. Urinary 3,5,6-trichloro-2-pyridinol (TCP) levels ranged from 9.42 to 1960 μg/g creatinine (*N*=271) and varied significantly by day of the week (GM range: 169–262 μg/g creatinine). Predictive models for chlorpyrifos air exposure and urinary TCP levels were developed using mixed-effects stepwise linear regression. Determinants of airborne chlorpyrifos exposure included minutes chlorpyrifos applied and enclosed crawl space treated (yes/no). Determinants of TCP levels (depending on the model) included day-of-the-week, the chlorpyrifos air concentration one and two days before urine collection, minutes of chlorpyrifos applied one and two days before urine collection, enclosed crawl space treated (yes/no), and commercial structure treated (time-weighted). Within- and between-worker variablity was similar for airborne chlorpyrifos; however, for TCP, between-worker variability exceeded within-worker variability by six times. The elimination half-life of TCP (26.9 h) and possibly the short sampling interval (one week) may explain the low TCP within-worker variability. Applicators' weekly mean ln(TCP levels) and weekly mean ln(chlorpyrifos air concentrations) were highly and positively linearly correlated (r^2=0.73, $P<0.0001$). In summary, mixed-effects models were successfully constructed to predict airborne chlorpyrifos exposure and urinary TCP levels. Published by Elsevier Science Ltd on behalf of British Occupational Hygiene Society

Keywords: chlorpyrifos; 3,5,6-trichloro-2-pyridinol; exposure determinants; mixed models; variance components; pesticide

INTRODUCTION

Chlorpyrifos [O,O-diethyl O-(3,5,6-trichloro-2-pyridinyl) phosphorothioate] is a widely used broad-spectrum organophosphorus insecticide. In 1995, an estimated 4–6 million kg were used for crop protection and another 5–8 million kg were used for non-agricultural purposes in the United States (US EPA, 1997). Use of chlorpyrifos as a termiticide increased following the removal of chlordane from the US market in 1988.

Chlorpyrifos exhibits moderate acute toxicity (Gallo and Lawryk, 1991), having a dose-dependent effect on depression of plasma cholinesterase, while red cell cholinesterase generally remains unaffected, except at high doses (Griffin *et al*., 1976; Richardson, 1995). Excessive exposure to chlorpyrifos can produce symptoms typical of acute organophosphorus poisoning (Hathaway *et al*., 1996). A morbidity study among manufacturing employees exposed to chlorpyrifos, although subject to several limitations, reported significantly elevated odds ratios for five diagnostic categories: diseases of the ear and mastoid process,

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acute respiratory infections, other diseases of the respiratory system, general symptoms, and general symptoms of the digestive system (Burns *et al*., 1998). Limited evidence of neurological effects attributable to chronic low-level exposure to chlorpyrifos has been reported (Ames *et al*., 1989; Kaplan *et al*., 1993; Steenland *et al*., 2000).

Chlorpyrifos is metabolically activated in the liver to chlorpyrifos oxon, which produces neurotoxicity by inhibiting target esterases in the peripheral and central nervous systems. The oxon is detoxified to diethyl phosphate and 3,5,6-trichloro-2-pyridinol (TCP) by A-esterases, such as paraoxonase, in the liver and plasma (Richardson, 1995). The mean urine elimination half-life of TCP in humans after administration of oral and dermal doses of chlorpyrifos has been estimated to be 26.9 h (Nolan *et al*., 1984). TCP excretion rates in occupationally exposed workers have been shown to be near maximum at 18–24 h post-exposure (Fenske and Elkner, 1990). In orally dosed rats, 88.4% of the administered chlorpyrifos was excreted in the urine, primarily as the glucuronide of TCP (Bakke *et al*., 1976).

The chlorpyrifos exposure of a group of termite control workers was monitored in this study. Termite control work is often an entry-level job and turnover among applicators tends to be high. Applicators typically work 8 h per day, Monday through Friday, and travel to multiple job sites within a day. In the Piedmont region of North Carolina, where this study was conducted, termite control work is typically heaviest from March through June, although some level of treatment work occurs throughout the year. Building construction, soil type and termite activity influence tasks performed by applicators. In this area, residences are predominately constructed with crawl spaces, although basement and slab construction are also found. Treatment tasks may include using an electric drill to create injection holes in concrete slabs or blocks, using hand tools to dig trenches in the soil around the perimeter of a structure, flooding trenches with a stream of termiticide from a hose, injecting or 'rodding' termiticide into the soil or injection holes, and patching drilled holes with mortar after treatment. Applicators tend to mix their own termiticides and to use an open mixing system; i.e. the applicator pours liquid termiticide product from a 7.57 l. plastic container into a 190–757 l. tank where it is diluted with water, typically to about 1% product. Termite treatment work in structures with enclosed crawl spaces can involve dirty and cramped conditions. Applicators may wear coveralls, gloves, eye protection, respirators and rubber boots. Mechanical ventilation is not used in crawl spaces. Applicators may be exposed to chlorpyrifos by inhalation and by skin absorption while mixing and applying termiticide solutions. Exposures from spills, while eating, drinking or smoking, and from contaminated objects are also possible.

Previous exposure assessment studies of termite control workers have involved small numbers of workers and have had limited ability to examine exposure factors in detail (Jitsunari *et al*., 1989; Fenske and Elkner, 1990; Leidy *et al*., 1991; Gibbons *et al*., 1993). The objectives of this study were (1) to characterize the chlorpyrifos exposures and work tasks of a group of termiticide applicators, and (2) to identify significant determinants of chlorpyrifos exposure and urinary TCP that could be used to build predictive models. For TCP, we were interested in developing models that addressed two data conditions; the first, when both air and work factor data are available, and the second, when only work factor data are available. Work factors that companies and their applicators could readily record or measure were especially of interest.

METHODS

Applicator recruitment

Using state records, pest control companies licensed to treat structures for wood-destroying pests were identified in 26 counties in the Piedmont region of North Carolina. Individual companies were contacted to determine if the company employed full-time termiticide applicators and if applicators used chlorpyrifos-containing termiticides. Permission was sought from companies meeting these criteria to recruit applicators for the study. Participation was voluntary and informed consent was obtained. Applicators were compensated $70 for full participation. This study was approved by the NIOSH Human Subjects Review Board.

Air sampling and analysis

We attempted to collect a full-shift breathing zone air sample on five consecutive workdays (Monday–Friday) for each applicator. No air sample was obtained on days an applicator was not at work. Samples were collected according to NIOSH Method 5600, Organophosphorus Pesticides (NIOSH, 1994) and analyzed for chlorpyrifos by DataChem Laboratories (Salt Lake City, UT). OSHA Versatile Samplers (OVS) with 11 mm quartz fiber filters and two sections of XAD-2 resin (SKC, Inc., Eighty Four, PA) were used at a nominal flow rate of 1 l./min. Sampling time included lunch and breaks. Sampling pumps were pre- and post-calibrated with a Gilibrator™ flow meter (Sensidyne, Inc., Clearwater, FL). Field blanks were collected in a similar manner, except no air was pulled through the sample.

Samples were inadvertently analyzed using two variations of the NIOSH method. In method variation no. 1, the quartz filter, the two sorbent sections, the polyurethane separator between front and back sorbent sections, the Teflon™ retaining ring for the filter, and a rinsate of the inside walls of the OVS tube were

analyzed, but only the quartz filter and two sorbent sections were analyzed in method variation no. 2. Components were desorbed or rinsed with 2 ml of 10:90 acetone:toluene and rotated at 6 rev/min for at least 1 h. Chlorpyrifos was determined on a Hewlett-Packard Model HP5890 gas chromatograph with a flame photometric detector in the phosphorus mode. A 30 m×0.25 mm fused silica capillary column coated internally with 0.25 μm DB-5 was used. The oven was initially set at 75°C for 2 min, then increased to 150°C at a rate of 50°C/min, followed by an increase to 210°C at a rate of 10°C/min. Two μl were injected at 250°C. The batch limit of detection (LOD), computed from linear regression of low level standards (Burkart, 1986), was 0.02–0.2 μg/sample (0.042–0.42 $\mu g/m^3$ for an 8 h sample at 1 l./min).

Urine sampling and analysis

Participants were asked to collect a first-morning urine void for seven consecutive days starting on Tuesday. Seven urine collection kits, each containing a plastic collection cup and pre-labeled sample bottles, were given to each participant. Each evening preceding sample collection, participants were asked to empty their bladder before going to bed. After voiding the next morning, participants poured approximately 25 ml of urine into a sample bottle and recorded the date and time of sample collection. On one of the seven days, a second sample was saved as a blind duplicate. All sample bottles were stored in a sealed plastic container in the participant's home freezer. After seven days, the frozen urine samples were retrieved from the participant, transported on dry ice, and stored at −20°C.

Urine samples were analyzed for TCP by Pacific Toxicology Laboratories (Woodland Hills, CA) using a method developed and validated by Dow AgroSciences (Olberding, 1997). Frozen urine samples were brought to 35°C in a water bath to dissolve any solids. After thorough mixing by shaking, a 1 ml aliquot of urine from each sample was fortified with 10 μl of 20 μg/l. $^{13}C_2{}^{15}N$ - 3,5,6 - TCP (in acetone) as an internal standard and 100 μl of concentrated (12 N) hydrochloric acid. The sample vials were sealed with Teflon™-lined caps and vortexed for 5–10 s. Samples were then hydrolyzed in an 80°C water bath for 60 min. After hydrolysis, samples were brought to room temperature and 1 ml each of 20% aqueous sodium chloride and 1-chlorobutane were added to each sample. Sample vials were then capped and vortexed for 10 min. After vortexing, samples were centrifuged for 5 min at 2700 rev/min. The top 1-chlorobutane layer was transferred to a 2 ml autosampler vial and 100 μl of the derivatizing agent *N*-methyl-*N*-(tertbutyldimethylsilyl)-trifluoroacetamide (MTBSTFA) was added to each autosampler vial. The samples were vortexed for 5–10 s, placed in an oven at 60°C for 60 min, and analyzed for TCP by gas chromatography with mass-selective detection as described below.

A Hewlett-Packard 6890 gas chromatograph (Wilmington, DE) equipped with a Hewlett-Packard 5973 mass-selective detector and a Durabond-17, 30 m×0.18 mm i.d., 0.3 film thickness, fused silica capillary column (J&W Scientific, Folsom, CA) was used for determination of TCP. The injection and interface temperatures were 280°C. An initial oven temperature of 80°C was held for 1 min, then ramped at 10°C/min to 180°C, followed by a second ramp at 20°C/min to 280°C where the temperature was held for 2 min. The carrier gas was helium. The mass-selective detector used electron impact ionization. Ions at $m/z = 254$ (quantitation) and $m/z = 256$ (confirmation) were monitored for the tert-butyldimethylsilyl (TBDMS) derivative of TCP, and an ion at $m/z = 261$ was used for the derivatized internal standard (TBDMS derivative of $^{13}C_2{}^{15}N$ - labeled TCP). The LOD, computed as three times the standard deviation of the blank (Keith *et al.*, 1983), was 2.0 μg/l.

Creatinine concentrations were determined by Pacific Toxicology Laboratories using a Beckman SYNCHRON LX™ System (Fullerton, CA). This system uses the Jaffé rate method in which creatinine forms a red color complex on reaction with picric acid under alkaline conditions (Fabiny and Ertingshausen, 1971). The LOD was 0.10 g/l.

Quality control

Quality control for the measurement of chlorpyrifos in air included (1) laboratory-fortified samples run blind by the analyst, (2) field-fortified samples submitted blind with field samples, and (3) laboratory-fortified samples exposed to ambient field conditions in a chlorpyrifos-free area and submitted blind with the field samples. Quality control for the measurement of TCP in urine consisted of (1) field-fortified samples submitted blind with field samples and (2) splits of selected field urine samples submitted as blind duplicates to the laboratory.

Other data collected

Demographic data, such as age and years worked as a termiticide applicator, were obtained by interview. During an applicator's sampled week, a number of factors were recorded for each termite treatment job performed using chlorpyrifos. These factors included areas treated, tasks performed, number of meters treated, duration of chemical application, product applied, product dilution, amount of diluted product applied, number of tank mixes prepared, use of personal protective equipment, hand washing, smoking, and chewing tobacco. An occupational hygienist accompanied the applicator during all work activities for the entire week and obtained information on the above factors by either direct measurement, observation or interview. In this paper, chlorpyrifos use is

computed and reported as kilograms of active ingredient.

Statistical analysis

Mixed-effects linear regression modeling was used to evaluate determinants of airborne chlorpyrifos exposure and urinary TCP levels. Mixed models have been used previously to investigate the fixed effects of covariates on levels of exposure and the within- and between-worker variance components associated with random worker effects (Rappaport *et al*., 1999; Burstyn *et al*., 2000; Symanski *et al*., 2001). The chlorpyrifos air concentration and the TCP urine concentration normalized to creatinine were used as dependent variables. These dependent variables were highly skewed and a natural log transformation was applied. Air sample values below the LOD were estimated by dividing the LOD by two (Hornung and Reed, 1990).

A stepwise regression procedure was done using PROC MIXED in SAS version 6.12 (SAS Institute, Inc., Cary, NC) to build linear models. One model was developed for chlorpyrifos and two models were developed for TCP, one of which included the chlorpyrifos air concentration. Subject was treated as a random effect. To address the correlation of measurements within subjects, two covariance structures, first-order autoregressive [AR(1)] and compound symmetry (CS), were evaluated in both the chlorpyrifos air models and the TCP urine models. Standard maximum likelihood estimation methods were used. Covariates with *P*-values greater than 0.10 were dropped from the models. Akaike's Information Criterion (AIC) was used to compare model fit among likely logical models. The within- and between-worker variance components were estimated from the random effects portion of the models. In order to obtain within- and between-worker variance estimates under an AR(1) covariance structure, both the REPEATED and RANDOM statements in PROC MIXED were used. Total variance was computed by fitting a model with only worker as a random effect (Burstyn *et al*., 2000).

Covariate values from the day the air sample was collected were used in air models and covariate values from days preceding urine collection were used in urine models. Chlorpyrifos exposures on Saturday and Sunday, and days a worker did not show up for work, were assumed to be zero. Three measures of chlorpyrifos use, kilograms, meters and minutes, were examined separately in the air and urine models. The measure that gave the best fit was used in subsequent regression models. For the selected measure of chlorpyrifos use (minutes), values the day before and two days before urine collection were tested separately in the models. Similarly, the chlorpyrifos air concentrations the day before and two days before urine collection were tested separately. Fixed effects in the final air model were excluded from the urine model that included the chlorpyrifos air concentration. A term for analytical method (1 or 2) was also tested in the air model.

Other continuous covariates tested in both the air and urine models included number of jobs performed, meters of enclosed crawl space treated, meters of outside perimeter treated, number of tank mixes prepared, square meters of broadcast spray, applicator age, years worked as a termiticide applicator, and years worked for current company. Treatment of an enclosed crawl space was also tested as a categorical variable (ever/never) and as a percentage of the total number of meters treated for the day (0–100). Categorical covariates that varied by job within a day were initially tested as 'ever/never' performed, and then weighted by the number of minutes of chlorpyrifos use to evaluate whether taking into account a measure of job size would improve the model. Covariates of this type in both the chlorpyrifos and TCP models included construction status (old/new), three tasks (flood-in-trench, rod-in-slab and rod-in-block), use of a helper, use of Dursban™ TC, and treatment of a commercial (i.e. non-residential) structure. Covariates of this type in the TCP models only included glove use during mixing and applying (tested separately), respirator use, wearing a coverall, rolling up long sleeves, and wearing robber boots. Smoking (yes/no), chewing tobacco (yes/no), and hand washing in the field (yes/no) were tested only as categorical variables in the TCP models.

RESULTS

Study population

A total of 155 companies licensed to treat structures for wood-destroying pests were identified. We were able to contact and describe the study to 117 companies (75%). The remaining companies either could not be reached or did not return phone calls. Of the 117 companies contacted, 61 (52%) were not eligible because the companies either did not use chlorpyrifos-containing termiticides or did minimal to no termite treatment work. Of the 56 eligible companies, 22 (39%) agreed to participate. The 22 companies had 49 full-time termiticide applicators. All 49 applicators consented to participate in the study. Forty-one applicators, all male, in 21 companies were eventually scheduled for sampling over the four-month study period from early March to early July, 1998. The activities of the applicators were monitored for a total of 202 applicator-days (38 applicators for five days each and three applicators for four days each). The median age was 33 years (range 18–54), the median number of years applicators had applied termiticides was 2 (range 0.1–28), and the median number of years applicators had worked for their current company was 1.2 (range 0.1–25).

The 41 applicators performed 415 termiticide application jobs using chlorpyrifos. One applicator

did not perform any chlorpyrifos termiticide applications during the sampled week. Characteristics of these jobs and the personal protective equipment used during application and mixing of chlorpyrifos-containing termiticides are given in Tables 1 and 2. For the 202 applicator-days, minutes of chlorpyrifos use was highly correlated with kg and meters of chlorpyrifos use ($r = 0.70$ and 0.58, respectively, $P = 0.0001$), and kg and meters of chlorpyrifos use were also highly correlated ($r = 0.68$, $P = 0.0001$). Pearson's coefficient was used to evaluate correlation between variables.

Table 1. Characteristics of termiticide treatment work with chlorpyrifos

		Frequency	
Building		By treatment job ($N = 415$)	
Construction			
New		116	
Old		299	
Design			
Residential		374	
Basement		25	
Crawl		219	
Slab		80	
Combination		50	
Commercial		41	
Process			
Product	*Dilution (%)*		
Dursban TC[a]	0.5	74	
	0.75	2	
	1	262	
	2	27	
Equity[a]	0.75	14	
	1	18	
Cyren TC[b]	1	15	
Other	0.10–0.25	3	
Number of loads mixed per job			
0		224	
1		174	
2		13	
3		4	
Tasks performed[c]			
Drill holes		161	
Rod in slab		155	
Rod in block		59	
Patch drill holes		115	
Dig trench		187	
Rod in trench or linear path		67	
Flood in trench or linear path		301	
Cover trench		125	
Personal protective equipment			
		Mixing ($N = 191$)	Applying ($N = 415$)
Gloves		94	305
Rubber boots		na[d]	38
Goggles		11	22
Safety glasses		8	22
Face shield		0	0
Apron		0	0
Cloth coveralls		37	111
Respirator use			
Any time during job		96	
Specific areas[e]			
Enclosed crawl space ($N = 137$ jobs)		59	
Inside basement ($N = 23$ jobs)		4	
Glove composition[f] ($N = 312$ jobs)			
Natural rubber, unlined		125	
Natural rubber, flock-lined		16	
Neoprene		55	
Nitrile		51	
Latex surgical		38	
Polyvinyl chloride		2	
Cloth		20	
Leather		5	

Continued overleaf

Table 1. Continued

		Frequency
		By applicator-day (N = 202)
Smoked tobacco		120
Chewed tobacco		7
Respirator type (N = 91 applicator-days)		
Half-face, pesticide cartridge		33
Half-face, organic vapor cartridge		10
Dust–mist disposable		6
Nuisance–odor disposable		42
Washed hands in field when chlorpyrifos used (N = 166 applicator-days)		110
Clothing		
Shirt	— long sleeves	48
	— short sleeves	154
Pants	— long pants	202
Hat		148
Jacket or sweatshirt (at least part of day)		54
Work shoes/boots	— leather	161
	— athletic	27
	— rubber	14

[a]Dow AgroSciences, Indianapolis, IN.
[b]Cheminova, Inc., Wayne, NJ.
[c]More than one task possible per job.
[d]na = not available.
[e]Respirator may have been worn in more than one area per job.
[f]Includes gloves worn while either mixing or applying chlorpyrifos.

Table 2. Chlorpyrifos usage

	N[a]	Median	AM[b]	SD[c]	Range
By job					
Linear meters treated with chlorpyrifos					
All jobs	415	48.8	61.3	64.6	0.3–637
By location					
Outside perimeter	242	42.7	39.9	29.3	0.3–177
Crawl space — enclosed	137	39.6	37.8	31.7	1.2–314
Pillars	103	14.6	16.5	11.3	1.2–28.0
Other	92	12.2	22.6	40.2	0.3–256
Garage — enclosed	55	19.5	18.3	8.5	1.2–9.8
Garage — open	42	22.3	25.6	12.8	12.8–88.4
Inside perimeter — enclosed	33	6.1	14.0	16.8	0.9–73.2
Crawl space — open	31	52.7	50.3	15.2	3.4–74.4
Inside basement	23	33.5	31.7	19.5	1.8–67.1
Inside perimeter — open	22	52.7	88.4	81.1	16.2–319
Broadcast spray (m^2)	50	26	270	928	0.4–6364
Time chlorpyrifos applied (min)	415	19	26	25	0.2–169
Amount of chlorpyrifos applied (kg)	415	0.9	1.3	1.4	0.02–11
By applicator-day					
Duration of workday (min)[d]	202	547	532	122	40–945
Linear meters treated with chlorpyrifos	166	114	153	148	1.5–901
Time chlorpyrifos applied (min)	166	56	66	42	0.7–201
Amount of chlorpyrifos used (kg)	166	2.5	3.3	2.9	0.07–15

[a]Total number of jobs = 415; total number of applicator - days = 202.
[b]AM = arithmetic mean.
[c]SD = standard deviation.
[d]Includes lunch and breaks.

Exposure levels

In total, 202 air samples were collected. Of these, 184 air samples were analyzed by method variation no. 1 (N = 110) and no. 2 (N = 74) The remaining 18 samples were excluded from data analysis due to gross analyst error (not analyzing the quartz filter). Three of the 184 samples (1.6%) were below the LOD. Chlorpyrifos was not found in any blanks. Geometric mean (GM) levels of chlorpyrifos by day of the week ranged from 8.9 to 11 $\mu g/m^3$, with an overall

GM of 10 μg/m^3 (Table 3). The highest single-day exposure to chlorpyrifos was 110 μg/m^3. Inhalation doses in μg/kg/day were also estimated (Appendix A).

Participants provided 285 urine samples. Field records indicated that the collection protocol was not followed by two participants and these samples ($N = 13$) were omitted from data analysis. An additional sample was omitted because the creatinine concentration was below the LOD and the sample was considered suspect. For the remaining 271 urine samples, GM TCP levels by day of the week ranged from 169 (Monday) to 262 μg/g creatinine (Friday) (Table 3). Levels for individual samples ranged from 9.42 to 1960 μg/g creatinine. TCP levels not normalized to creatinine ranged from 21.3 to 3260 μg/l. Applicators' weekly mean ln(TCP levels) and weekly mean ln(chlorpyrifos air concentrations) were highly and positively linearly correlated (Fig. 1, $r^2 = 0.73$, $P<0.0001$).

For all analytes and types of quality control sample, mean recoveries ranged from 95 to 103% and mean relative standard deviations were 10% or less (Table 4).

Exposure models

Chlorpyrifos air model. A linear model for airborne chlorpyrifos exposure (Table 5) was built using data from the 37 workers with an appropriately analyzed air sample (184 applicator-days). A compound symmetric covariate structure was assumed as it produced better fit than first-order autoregressive. Minutes of chlorpyrifos application on the day the air sample was collected and whether or not the applicator treated at least one enclosed crawl space were significantly associated with increased exposure to airborne chlorpyrifos. All other covariates, including analytical method, were not significant ($P>0.1$).

TCP urine models. Two linear models were developed for TCP (Table 6). The first, Model A, included the chlorpyrifos air concentration and the second, Model B, did not. Model A included data from 35 applicators (173 applicator-days) who had both airborne chlorpyrifos and urinary TCP levels. Model B included Tuesday through Saturday urinary TCP data from 39 applicators (194 applicator-days). A first-order autoregressive covariate structure was assumed as it produced better model fit than compound symmetry. A significant day-of-the-week effect was found in both models, although less so in Model A. TCP levels were significantly ($P<0.05$) lower on Tuesday, Wednesday and Thursday as compared with Saturday in Model B, whereas in Model A, TCP levels were significantly lower on Wednesday as compared with Saturday, and marginally lower on Tuesday ($P = 0.107$) and Thursday ($P = 0.072$). TCP levels on Friday and Saturday were essentially similar ($P>0.9$) in both models.

In Model A, the chlorpyrifos air concentrations one and two days before the urine sample was collected and treatment of a commercial structure weighted by the minutes of chlorpyrifos use on the job were associated with increased TCP levels. A model was also constructed using one day of air sampling; however, model fit was reduced (i.e. higher AIC value) as compared with the model with two days of air sampling. In Model B (air concentration not in model), both minutes of chlorpyrifos application one and two days before urine collection, treatment of an enclosed crawl space (yes/no), and treatment of a commercial

Table 3. TCP in urine and chlorpyrifos in air levels by day of week

Day	*N*	AM[a]	SD[b]	GM[c]	GSD[d]	Range
Analyte: TCP (μg/g creatinine)[e]						
Tuesday	39	272	205	183	2.89	9.42–9.38
Wednesday	38	287	201	210	2.53	22.3–1050
Thursday	39	319	252	228	2.51	19.5–1310
Friday	39	378	293	262	2.68	19.1–1390
Saturday	39	380	338	258	2.77	11.1–1960
Sunday	38	341	306	218	3.00	10.1–1610
Monday	39	247	206	169	2.75	9.69–1110
Analyte: chlorpyrifos (μg/m^3)[f]						
Monday	37	19	21	11	3.1	0.59–84
Tuesday	37	16	13	10	3.4	<0.048[g]–59
Wednesday	37	17	20	8.9	3.8	<0.19–85
Thursday	37	19	23	11	3.0	0.87–110
Friday	36	23	26	10	4.2	<0.10[g]–100

[a]AM = arithmetic mean.
[b]SD = standard deviation.
[c]GM = geometric mean.
[d]GSD = geometric standard deviation.
[e]First-morning urine void.
[f]For all samples ($N = 184$), AM = 19 μg/m^3, SD = 21 μg/m^3, GM = 10 μg/m^3, GSD = 3.5.
[g]Less than the LOD. The LOD varied by batch and by sample air volume.

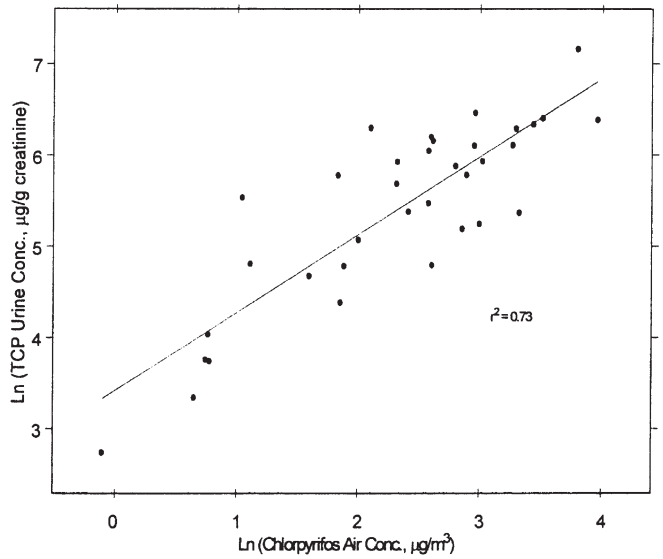

Fig. 1. Exposure–biomarker relationship for 35 termiticide applicators exposed to chlorpyrifos. Each point represents the estimated mean value of TCP (raw data given in µg/g creatinine) for an applicator, plotted versus the estimated mean air exposure (raw data given in µg/m^2) for that applicator (slope = 0.854, intercept = 3.42, $r^2 = 0.73$, $P<0.0001$).

Table 4. Quality control results

Analyte	*N*	Range[a]	Mean recovery (%)	Mean RSD[b] (%)
TCP in urine				
Laboratory	80	11.1–2890[c,d]	95.8	10
Field spike	21	26.2–2470[c,d]	95.3	6.0
Field duplicates	33	27.3–2090[e]	NA [f]	3.1
Creatinine in urine				
Laboratory	34	0.95–2.62[d]	96.5	2.2
Field duplicates	33	0.9–3.7[e]	NA	2.7
Chlorpyrifos in air				
Laboratory	27	2.5–40[d]	103	3.6
Field spike — not exposed to ambient conditions	18	1.8–28[d]	102	12
Field — exposed to ambient conditions	18	1.8–28[d]	100	6.3

[a]TCP in µg/l., creatinine in g/l., chlorpyrifos in µg.
[b]RSD = relative standard deviation.
[c]Background-adjusted nominal concentration.
[d]Fortification range.
[e]Range of levels found.
[f]NA = not applicable.

Table 5. Parameters of the chlorpyrifos-in-air regression model

Model[a,e]	β[b]	SE[c]	*P*-value
Dependent variable: ln(chlorpyrifos, µg/m^3) (*N* = 184 applicator-days, 37 workers)			
Intercept	1.715	0.171	<0.001
Minutes chlorpyrifos applied[d]	5.776×10^{-3}	1.582×10^{-3}	<0.001
Enclosed crawl space treated (yes/no)	0.608	0.135	<0.001

[a]Compound-symmetric covariance structure assumed.
[b]β = regression coefficient.
[c]SE = standard error.
[d]Day air sample collected.
[e]Example calculation where minutes chlorpyrifos applied=56 and enclosed crawl space treated=yes: µg/m^3 chlorpyrifos = exp[1.715 + ($5.776\times10^{-3}\times56$) + (0.608×1)] = 14.

Table 6. Parameters of the TCP-in-urine regression models

Model	β[b]	SE[c]	*P*-value
Dependent variable: ln(TCP, μg/g creatinine)			
A. Air concentration in model[a,j]			
(*N*=173 applicator-days, 35 workers)			
Intercept	5.145	0.183	<0.001
Day of the week[d] (4 DF[e] test, *P*=0.041)			
Tuesday	−0.185	0.114	0.107
Wednesday	−0.190	7.213×10^{-2}	0.009
Thursday	−0.119	6.541×10^{-2}	0.072
Friday	5.470×10^{-3}	5.164×10^{-2}	0.916
Saturday	0[f]		
ln(chlorpyrifos air concentration, μg/m^3)[g]	0.102	2.363×10^{-2}	<0.001
ln(chlorpyrifos air concentration, lagged 1 day, μg/m^3)[h]	6.144×10^{-2}	2.442×10^{-2}	0.013
Commercial structure treated, time-weighted[g,i]	0.183	9.012×10^{-2}	0.044
B. Air concentration not in model[a,k] (*N*=194 applicator-days, 39 workers)			
Intercept	5.333	0.157	<0.001
Day of the week[d] (4 DF[e] test, *P*<0.001)			
Tuesday	−0.327	7.405×10^{-2}	<0.001
Wednesday	−0.227	6.632×10^{-2}	<0.001
Thursday	−0.148	5.865×10^{-2}	0.013
Friday	-5.562×10^{-3}	4.551×10^{-2}	0.903
Saturday	0[f]		
Minutes chlorpyrifos applied[g]	1.953×10^{-3}	5.152×10^{-4}	<0.001
Minutes chlorpyrifos applied, lagged 1 day[h]	1.475×10^{-3}	5.073×10^{-4}	0.004
Enclosed crawl space (yes/no)[g]	0.109	3.803×10^{-2}	0.005
Commercial structure treated, time-weighted[g,i]	0.170	8.630×10^{-2}	0.050

[a]First-order autoregressive covariance structure assumed.
[b]β=regression coefficient.
[c]SE=standard error.
[d]Urine sample collected the morning of the indicated day.
[e]DF=degrees of freedom.
[f]Each day is compared with Saturday.
[g]Applies to 1 day before urine sample collected.
[h]Applies to 2 days before urine sample collected.
[i]Each job with a commercial structure was weighted by the number of minutes of chlorpyrifos application to account for differences in job size. Expressed as a proportion (0-1).
[j]Example calculation where day of the week urine sample is collected = Thursday, chlorpyrifos air concentration on Wednesday = 11 μg/m^3, chlorpyrifos air concentration on Tuesday = 11 μg/m^3, and proportion of time spent treating a commercial structure = 0.25: μg/g creatinine TCP = $\exp\{5.145 - (0.119 \times 1) + [0.102 \times \ln(11)] + [6.144 \times 10^{-2} \times \ln(11)] + (0.183 \times 0.25)\} = 236$.
[k]Example calculation where day of the week urine sample is collected = Thursday, minutes chlorpyrifos applied on Wednesday = 56, minutes chlorpyrifos applied on Tuesday = 56, enclosed crawl space treated = yes, and proportion of time spent treating a commercial structure = 0.25: μg/g creatinine TCP = $\exp[5.333 - (0.148 \times 1) + (1.953 \times 10^{-3} \times 56) + (1.475 \times 10^{-3} \times 56) + (0.109 \times 1) + (0.170 \times 0.25)] = 252$.

structure (time-weighted) were associated with increased TCP levels. All other covariates were not significant (*P*>0.1) in these two models. The interactions between minutes of chlorpyrifos use and glove use, and between minutes of chlorpyrifos use and respirator use, were highly non-significant in Model B (*P*>0.7).

Exposure variability. Variance component estimates are presented in Table 7. Error-bar plots illustrating within- and between-worker variability for chlorpyrifos air exposure and urinary TCP are shown in Fig. 2. Over the one-week sampling period, within-worker variability appeared to be higher for chlorpyrifos in air than for TCP in urine (Fig. 2) and the proportion of the within-worker variability to the total variability was lower for TCP in urine as compared with chlorpyrifos in air (Table 7). The within-worker and between-worker variance estimates were similar for airborne chlorpyrifos exposure (Table 7); however, for TCP, the between-worker variance estimate was approximately six times larger than the within-worker variance estimate in both urine models (Table 7). The percentage of the total variance explained by fixed effects varied by model (range 13–28) and in each model the fixed effects explained a substantially smaller percentage of the total variance than the random effects. The percentage of the total variance explained by fixed effects was approximately twice as high in urine Model A (with air concentration) than in urine Model B (without air concentration), although differences in sample size may be a factor when comparing these models. When only one day of air sampling was included in Model A, the percent-

Table 7. Variance components for the air and urine regression models

Model[a]	${}_{T}S_y^{2b}$	${}_{W}S_y^{2c}$ (%)[d]	${}_{W}$GSD[e]	${}_{B}S_y^{2f}$ (%)[d]	${}_{B}$GSD[g]	${}_{F}S_y^{2h}$ (%)[d]	$\hat{\rho}$[i]	$\hat{R}_{0.95B}$[j]
Air	1.53	0.59 (39)	2.2	0.68 (44)	2.3	0.26 (17)	NA[k]	26
Urine — Model A	1.15	0.12 (10)	1.4	0.72 (63)	2.3	0.32 (28)	0.61	26
Urine —- Model B	1.03	0.12 (12)	1.4	0.78 (76)	2.4	0.13 (13)	0.66	31

[a]Includes worker, fixed effects and intercept.
[b] ${}_{T}S_y^2$ = estimated total variance from a model containing only worker as a random effect.
[c] ${}_{W}S_y^2$ = estimated variance of the within - worker distribution.
[d]Percentage of the estimated total variance.
[e] ${}_{W}$GSD = estimated geometric standard deviation of the within - worker distribution.
[f] ${}_{B}S_y^2$ = estimated variance of the between - worker distribution.
[g] ${}_{B}$GSD = estimated geometric standard deviation of the between - worker distribution.
[h] ${}_{F}S_y^2$ = estimated variance explained by fixed effects.
[i] $\hat{\rho}$ = estimated lag−one autocorrelation.
[j] $\hat{R}_{0.95B}$ = exp[3.92 ln(GSD$_B$)] = ratio of the 97.5th and 2.5th percentiles of the between - worker distribution.
[k]NA = not applicable.

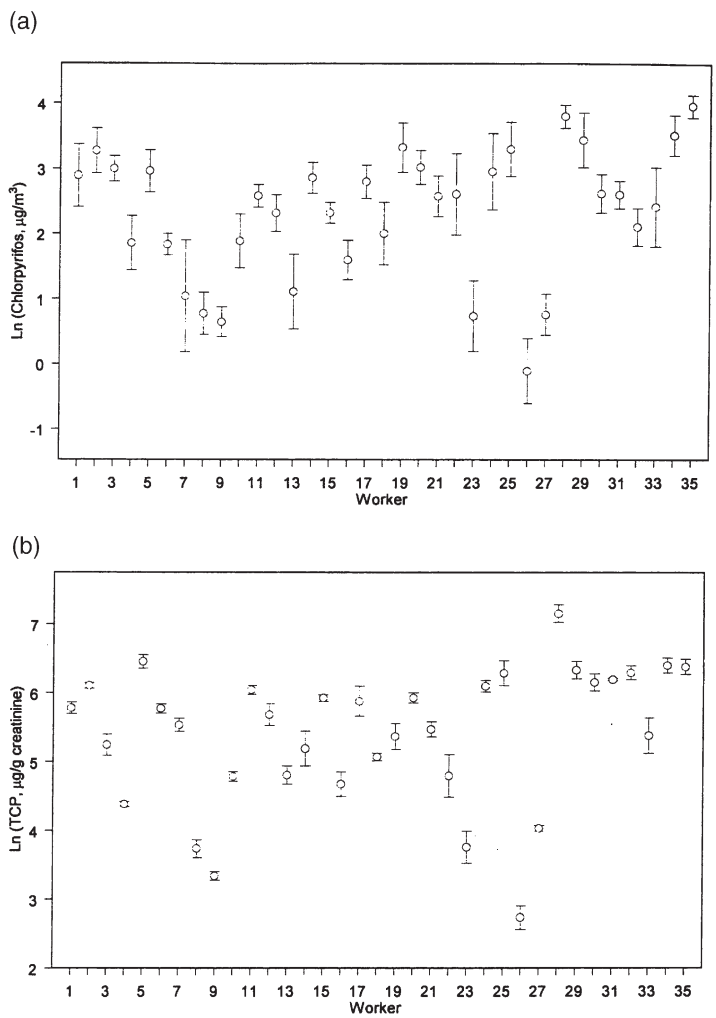

Fig. 2. Chlorpyrifos exposure (A), (µg/m^3), and TCP levels in urine (B), (µg/g creatinine), for 35 temiticide applicators. Estimated mean values and standard errors are shown. Error bars represent ±1 standard error of the mean exposure. Within each worker, $n = 5$ for both chlorpyrifos and TCP, except for workers 11 and 13, where $n = 4$ for both chemicals.

age of the total variance explained by fixed effects decreased to 19% (model not shown).

DISCUSSION

Airborne chlorpyrifos exposures and urinary TCP levels were readily measured in this population of termiticide applicators. Full-shift arithmetic mean chlorpyrifos air exposures were approximately 50% higher than those reported by Fenske and Elkner (1990). Exposures did not exceed the ACGM- and NIOSH-recommended 8 h time-weighted average chlorpyrifos occupational exposure limit of 200 μg/m^3 (ACGIH, 2000; NIOSH, 1992); however, the highest exposure (110 μg/m^3) was 55% of the limit.[1] It should be noted that 22% ($N = 40$) of the sampling times exceeded 10 h. The application of exposure limits intended for 8 h work days may not be appropriate for longer days. Also, these exposure limits may not be sufficiently protective if dermal absorption was significant.

TCP levels were generally in the same range reported by Jitsunari *et al*. (1989) for six workers, but could not be compared directly to results reported by Fenske and Elkner (1990) and Gibbons *et al*. (1993) because their data are expressed as excretion rates or total mass excreted per day, respectively. Given a TCP urine elimination half-life of 26.9 h (Nolan *et al*., 1984), if a worker absorbed the same chlorpyrifos dose every day for five days (Monday through Friday), TCP levels in the urine would reach steady state on Thursday, Friday and Saturday, assuming the worker started the week with no TCP in the urine. Although the chlorpyrifos dose workers absorbed each day in this study could not be controlled by investigators, GM TCP levels by day of week followed this predicted kinetic profile.

In two general population studies, TCP has been detected in the urine of 82% and 96% of US adults, with mean levels of 3.1 and 5.8 μg/g creatinine, respectively (Hill *et al*., 1995; MacIntosh *et al*., 1999). These TCP levels are presumably related to dietary and non-occupational exposures to chlorpyrifos and to TCP residues. TCP levels in all applicator urine samples exceeded these values by an average factor of 70. TCP is also a major metabolite of chlorpyrifos-methyl and a minor metabolite of triclopyr (Aprea *et al*., 1997; Carmichael *et al*., 1989); however, applicators in this study did not use these compounds while being monitored at work. TCP levels similar to those found here have been associated with decrements in a few subclinical tests of neurological function and in some self-reported physical and psychological symptoms; however, no clinical effects have been reported (Steenland *et al*., 2000).

The highly significant association between duration of chlopryrifos application and increased levels of chlorpyrifos in air and TCP in urine may be related to the manual application of chlorpyrifos-containing solutions using open delivery systems. The association between duration of chlorpyrifos application, lagged one day and increased TCP levels is consistent with the urinary elimination half-life of TCP, i.e. TCP levels in the urine should reflect chlorpyrifos exposure over 2–3 days. Treating an enclosed crawl space was most likely an important predictor of increased airborne chlorpyrifos exposure because these spaces have limited access and, therefore, poor natural ventilation. In both TCP models, treatment of a commercial structure, weighted by the number of minutes of chlorpyrifos use, was a determinant of increased TCP levels. The explanation for this association is not readily apparent. Approximately 10% of the treatment jobs involved commercial structures and less focus was placed on recording characteristics that may have varied between these structures and residential structures.

We were not able to show an association between respirator or glove use and TCP levels, nor did we find a significant interaction between respirator or glove use and minutes of chlorpyrifos application, a highly significant predictor of TCP in Model B. Applicators were approximately four times as likely to wear a respirator, and approximately two times as likely to wear gloves when treating enclosed crawl spaces as compared with treating other spaces. The preferential use of respirators in enclosed crawl spaces as compared with other spaces is most likely related to a regulatory requirement to wear respirators in non-ventilated spaces. Proper respirator and glove use should result in decreased TCP levels if exposure is via inhalation (respirators) or via the hands (gloves). Even though applicators wore respirators and gloves on some jobs, it is possible that the devices or the manner of use did not provide the expected protection. Absence of a respirator effect could also occur if a substantial portion of the exposure was dermal. Similarly, lack of a glove effect could occur if exposure was mostly by inhalation or if dermal exposure was via body areas other than the hands.

The strength of the correlation between chlorpyrifos exposure in air and TCP in urine, as well as a straight-line slope of the log–log relationship that was close to unity ($r^2 = 0.73$, slope = 0.854, Fig. 1), suggest that TCP is a useful biomarker of chlorpyrifos exposure and that linear (first-order) kinetics prevailed (Rappaport *et al*., 1995). This relationship does not exclude the possibility of a significant correlation between dermal exposure and TCP and does not indicate the magnitude of any dermal contribution to exposure, which was not evaluated in this study. In

[1] Editorial note: ACGIH have given notice of intent to change their TLV for chlorpyrifos to 100 μg/m^3 inhalable particulate in 2001.

a very small study of termiticide applicators using chlorpyrifos (7 measurements), Fenske and Elkner (1990) found that dermal dose, but not respiratory dose, was significantly correlated with TCP for certain urine collection intervals over a 72 h period. They estimated that 73% of the total absorbed daily dose was by the dermal route, although two of three workers who spent time in a crawl space and one worker who conducted clean-up in an enclosed space were estimated to receive 40–45% and 48% of the estimated dose by inhalation, respectively. Our findings and those of Fenske and Elkner (1990) indicate that for termiticide application work, especially work involving crawl spaces, inhalation exposure should not be ignored.

The low within-worker variability for TCP may be related to 'physiological damping', i.e. the attenuation of exposure variability in the body associated with the elimination half-life of a substance (Roach, 1966; Rappaport, 1985; Rappaport and Spear, 1988). It may also be related to the short sampling interval in this study (one week). Perhaps greater within-worker variability would have been found if sampling had been conducted over the course of a year. Metabolic differences between individuals may explain some of the between-worker TCP variability (Blatter Garin *et al*., 1997).

Applicators preferred short-sleeved shirts, even though long-sleeved shirts were required. This preference may be related to comfort in the heat. Complaints about goggles fogging up were common and may explain limited protective eyewear use. Interestingly, applicators were more likely to wear gloves while applying diluted product than while preparing tank mixes with concentrated product. Coverall use was most likely higher during application than during mixing to protect work clothes in dirty crawl spaces.

This study has limited generalizability. Applicators were recruited from a specific region of North Carolina and it is not known if termiticide applicators at non-participating companies were substantially different from study applicators. Also, only exposures during March to July were measured, reportedly a busy time of year. Dermal exposure data would have been desirable for a more complete characterization of exposure routes. Although applicators predominately used chlorpyrifos for termite treatment work, on 7% of the sampled work days, applicators used a chlorpyrifos-containing product for other purposes, such as general pest control or lawn care. Five applicators may have used some chlorpyrifos on Saturday. Potential sources of chlorpyrifos exposure that occurred infrequently, such as leaks from hoses and pumps, spills, thawing tanks with kerosene heaters, rinsing jugs, and installing crawl space vapor barriers or vents after treatment, were not evaluated as exposure determinants.

In summary, the GM exposure of termiticide applicators to airborne chlorpyrifos was approximately 5% of the recommended occupational exposure limit, while individual exposures ranged up to 55% of the limit. GM TCP levels were lowest on Monday and reached a plateau on Friday and Saturday. Significant determinants of airborne chlorpyrifos exposure and TCP levels included the duration of chlorpyrifos application and the type of space treated. In the TCP models, day of the week and the chlorpyrifos air concentration were also significant determinants. These findings suggest that control measures aimed at reducing chlorpyrifos air exposures, especially in enclosed crawl spaces (e.g. portable mechanical ventilation) or changes in application technique that reduce the duration of chemical handling, would lead to lower TCP levels in the body. We were not able to show that respirator or glove use affected TCP levels; however, applicators were more likely to wear protective equipment when treating enclosed crawl spaces, itself a predictor of exposure, and therefore some confounding is possible. Within- and between-worker variability was similar for airborne chlorpyrifos; however, for TCP, between-worker variability exceeded within-worker variability by six times.

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APPENDIX A

Inhalation dose estimates by category of applicator-day

Applicator-day category	N[a]	Inhalation rate[b] (m^3/h)	Estimated inhalation dose[c] (μg/kg/day)		
			AM (±SD)	GM (GSD)	Range
Only post-construction jobs	128	1.74	3.6 (±4.3)	1.5 (5.0)	0.0035–24
Only pretreat (new) construction jobs	15	1.5	2.1 (±1.7)	1.6 (2.1)	0.42–7.1
Mix of pre- and post-treat construction jobs	41	1.62	3.4 (±3.2)	2.4 (2.3)	0.58–14

[a]Number of applicator-days.
[b]Inhalation uptake assumed to be 100%. Inhalation rates from US Environmental Protection Agency revised risk assessment for chlorpyrifos (US EPA, 1999).
[c]Body weight self-reported.