

Comparative Analysis of Passive Dosimetry and Biomonitoring for Assessing Chlorpyrifos Exposure in Pesticide Workers

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Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), the US Environmental Protection Agency (EPA) has the authority to regulate the use of pesticides to prevent unreasonable adverse human health effects associated with pesticide exposure. Accordingly, the EPA requires pesticide registrants to perform studies evaluating the potential for pesticide handler exposure. Data from five such studies that included exposure measurements based on both external measurements and biological monitoring were used to examine methods of assessment, routes and determinants of exposure and dose to the pesticide chlorpyrifos. Eighty workers across four job classes were included: mixer/loaders (M/L, $n = 24$), mixer/loader/applicators (M/L/A, $n = 37$), applicators (A, $n = 9$) and re-entry scouts (RS, $n = 10$). Results showed that doses were highly variable and differed by job class ($P < 0.05$) with median total (inhalation and dermal combined) exposure-derived absorbed doses (EDAD_{tot}) of 129, 88, 85 and 45 µg/application for A, M/L/A, M/L and RS, respectively. Doses derived from the measurement of 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) in urine were similar in magnitude but differed in rank with median values of 275, 189, 122 and 97 µg/application for A, M/L, RS, and M/L/A, respectively. The relative contribution of dermal to inhalation exposure was examined by their ratio. The median ratios of exposure-derived absorbed dermal dose (EDAD_{derm}) (assuming 3% absorption) to exposure-derived absorbed inhalation dose (EDAD_{inh}) (assuming 100% absorption) across job classes were 1.7, 1.5, 0.44 and 0.18 for RS, M/L, A and M/L/A, respectively, with an overall median of 0.6. For 34 of 77 workers (44%), this ratio exceeded 1.0, indicating the significance of the dermal exposure pathway. Different dermal absorption factor (DAF) assumptions were examined by comparing EDAD_{tot} to the biomarker-derived absorbed dose (BDAD) as a ratio where EDAD_{tot} was calculated assuming a DAF of 1, 3 and 10%. Median ratios of 0.45, 0.71 and 1.28, respectively, were determined suggesting the DAF is within the range of 3–10%. A simple linear regression of urinary 3,5,6-TCP against EDAD_{tot} indicates a positive association explaining 29% of the variability in the 3,5,6-TCP derived estimate of dose. A multiple linear regression model including the variables EDAD_{derm}, EDAD_{inh} and application type explained 46% of the variability ($R^2 = 0.46$) in the urinary dose estimate. EDAD_{derm} was marginally significant ($P = 0.066$) while EDAD_{inh} was not ($P = 0.57$). The EDAD_{derm} regression coefficient (0.0007) exceeded the coefficient for EDAD_{inh} (0.00002) by a factor of 35. This study demonstrates the value of the pesticide registrant database for the purpose of evaluating pesticide worker exposure. It highlights the significance of the dermal exposure pathway and identifies the need for methods and research to close the gap between external and internal exposure measures.

Keywords: chlorpyrifos; dermal; exposure assessment; whole body dosimetry; biological monitoring; inhalation; pesticides

INTRODUCTION

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Public health concern about occupational exposure to pesticides began after the introduction of the acutely

toxic organophosphate insecticides in the late 1940s. Since then, many additional incidents of pesticide poisoning have been observed in agricultural workers [Mehler *et al.*, 1992; Center for Disease Control and Prevention (CDC, 1998); Das *et al.*, 2001]. Concerns about the potential hazards to farm workers remain today. The Environmental Protection Agency (EPA) estimates that ~10 000–20 000 (0.8%) of the 2.25 million agricultural workers in the United States suffer from acute pesticide poisoning annually (USEPA, 1992a,b). Others have reported as many as 300 000 acute illnesses and injuries of farm workers due to pesticide exposures (USGAO, 1993). According to the US Bureau of Labor Statistics, farm workers experience the highest rate of chemical-related illness of any occupational group (5.5 cases per 1000 workers) (US Bureau of Labor Statistics, 1987). According to the California Pesticide Illness Surveillance Program, 914, 804 and 656 cases of pesticide illness or injury associated with occupational exposure occurred in the years 1998, 1999 and 2000, respectively (California EPA, 2000, 2001, 2002). Pesticide illness and injury surveillance programs in Florida, Texas and New York reported 171, 154 and 16 cases of acute occupational pesticide-related illness in 1999, respectively (NIOSH, 2000).

The widespread health impacts of pesticide use prompted the promulgation of the Worker Protection Standard of the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) in 1992 [Code of Federal Regulations (CFR, 2002)] to protect agricultural workers. Under this Act, the EPA is charged with reducing the risks of illness or injury resulting from occupational exposures to pesticides. To meet this provision of FIFRA, the EPA has implemented a registration process that requires pesticide manufacturers (registrants) to submit studies evaluating occupational exposures to pesticide handlers. Information gathered from these studies such as pesticide formulation, pesticide application rate, and exposure estimates is compiled in the EPA's Pesticide Registrant Database. This database provides a wealth of information by which to explore the reliability and reproducibility of exposure assessment measurements. Registration requirements and recommendations for exposure monitoring can be found in the Office of Prevention, Pesticides, and Toxic Substances' harmonized guidelines 875 Series, Occupational and Residential Exposure Test Guidelines (USEPA, 1998). These guidelines include specific methods for passive dosimetry and biological monitoring to assess worker exposure so that there is general uniformity across studies.

The assessment of dermal exposure to pesticides in workers is both complex and important. A number of studies have established that the dermal route can contribute as much or more to a worker's exposure than inhalation (Wolfe, 1976; Fenske *et al.*, 1989; Fenske and Elkner, 1990; Woollen, 1993; Cattani

et al., 2001). Although methods for evaluating inhalation exposure including the use of personal air monitoring are reasonably well standardized, such is not the case for dermal exposure, where there is a lack of consensus regarding a wide range of methods with differing underlying assumptions (Fenske, 1993; Hendersen *et al.*, 1993; Krieger, 1995; USEPA, 1998). The EPA recommends that registrant studies be conducted using whole body dosimetry (WBD) for assessing pesticide worker dermal exposure. Although there are recognized limitations to this methodology, including its adequacy to serve as a skin surrogate and assumed uniform absorption across body regions, it is thought to provide the best external means for assessing dermal exposure (Fenske, 1993; Ness, 1994; USEPA, 1998). In light of the limitations, the EPA recommends that biological monitoring be used in combination with WBD to provide a complimentary assessment of exposure. Biological monitoring captures the chlorpyrifos pesticide penetrating the dosimeter and absorbed through the skin, and that which is inhaled (including the penetration of respiratory protection), as well as non-dietary ingestion. The comparison of exposure with biological monitoring is most informative when parameters of human metabolism and pharmacokinetics are characterized and available (Chester, 1993; Woollen, 1993; Krieger, 1995).

Chlorpyrifos has been selected for a case study because of its prevalent use (USEPA, 1988, 2000; Albers *et al.*, 1999), toxicity (USEPA, 1988, 2000; Albers *et al.*, 1999), and quality and completeness of data among the registrant studies. Chlorpyrifos is extensively used in agriculture and is also applied to pastures and woodlands. An estimated 20–24 million pounds of chlorpyrifos are expected to be applied annually (USEPA, 2000). Chlorpyrifos is a cholinesterase inhibitor associated with many neurophysiological effects such as nausea, dizziness and confusion, and, at high exposures, respiratory paralysis and death (USEPA, 2000). Because of toxicity and exposure concerns with residential use, the EPA negotiated with manufacturers to voluntary phase-out its residential use in the year 2000. The EPA also lowered tolerances on certain crops, such as apples and tomatoes (USEPA, 2000).

A number of pesticide registrant studies have been conducted employing a combination of methodologies including WBD and biological monitoring. These studies may hold valuable data to estimate the importance of specific exposure routes and determinants and to evaluate the performance of assessment methods. Accordingly, the goals of the current study are to: (i) demonstrate the research value and utility of the registrant database for investigating worker exposure; (ii) characterize worker chlorpyrifos exposure and examine the relative contribution of dermal and inhalation routes; (iii) identify exposure determinants; and (iv) provide an estimate of the dermal absorption

factor. As a result, this study will provide an improved understanding of worker exposure and methods of assessment as a fundamental basis for health protection.

METHODS

Among the approximately 100 registrant studies on file with the EPA, five were selected for analysis (Table 1). These studies were subject to EPA's internal review requirements including an approved human studies protocol and informed consent (USEPA, 1991). Studies were selected based on the following criteria: (i) workers were exposed to the pesticide chlorpyrifos; (ii) exposure was assessed based on the EPA's 1998 Guidelines; (iii) biological monitoring was included; and (iv) results and methods were complete and sufficiently detailed. Individual exposure data as well as information regarding methodology of the studies were extracted, pooled, and entered into ExcelTM spreadsheets. Four different job categories were represented across the five studies including: mixer/loaders (M/L), applicators (A), re-entry scouts (RS) and mixer/loader/applicators (M/L/A). The M/L is responsible for preparing the pesticide and loading it into the application equipment, while the Applicator applies the pesticide. The M/L/A performs both job functions. The RS enters the field following pesticide application to assess the effectiveness of the treatment. EPA's exposure assessment guidelines (USEPA, 1998) were followed for each of the five studies. The number of workers monitored per study ranged from 5 to 28. Each worker was monitored once over a period of time representing a standard work shift or duration of application.

Inhalation exposure was evaluated by personal monitoring capturing both gas and particle phase chlorpyrifos in the workers' breathing zone. Samples were collected on a 37 mm mixed cellulose ester filter (0.8 μm pore size) (Gelman Sciences, Ann Arbor, MI) placed upstream to a 99 mg ChromosorbTM 102 adsorbent tube (SKC, Inc., Eighty Four, PA) and connected to the tube by a glass funnel and rubber tubing. The filter cassette and tube assembly were connected by flexible TygonTM tubing to a battery-powered personal sampling pump (SKC, Inc.,) operating at a flow rate of 1–2 l/min that was pre- and post-calibrated with a rotameter. Sample durations ranged from 0.5 to 9 h. Sample volumes ranged from 0.0209 to 0.788 m^3 . The front and back sections of the tubes were extracted separately. Samples were analyzed by gas chromatography combined with an electron capture detector.

Dermal exposure was assessed using WBD including handwash samples in all five studies. The dosimeter consisted of underclothing in the form of

a short-sleeved T-shirt and briefs. All workers wore cotton coveralls. Six wore additional full rain gear, while 10 workers had short-sleeved coveralls rather than long. In all but one study, a ball cap was worn as a dosimeter to estimate exposure to the neck and head. In the study by Contardi *et al.* (1996), either a cap or two headbands (one on the head, one on the neck) was used to estimate dermal exposure to the head. The coveralls and underclothing were cut into pieces representing potential exposure to body regions such as the arms, legs, and front and back torso. Chlorpyrifos was extracted from the clothing. The amount of chlorpyrifos found on the underclothing relative to the amount on the coveralls was used to estimate individual site-specific penetration factors (PFs), i.e. the percentage of chlorpyrifos passing through the coveralls to the skin. These penetration factors were used to estimate dermal exposure to arm and leg regions where no undergarment was present.

Handwash samples were collected over the monitoring period during times when workers would typically wash their hands (i.e. before meals, before smoking, after using the bathroom and at the end of the monitoring period) to assess surface deposition on the hands. Handwash samples were also collected between tasks to note differences in task contribution. The amount of chlorpyrifos found on the hands was then added to the amount measured with WBD to obtain the total dermal exposure (TDE) (μg chlorpyrifos). A dermal absorption factor (DAF) of 3% was applied to the TDE to obtain an exposure-derived absorbed dermal dose (EDAD_{derm}) value (μg chlorpyrifos), as is shown in equation (1). The DAF is 3%, based on human studies by Nolan *et al.* (1994) and is the value accepted by the EPA.

$$\text{EDAD}_{\text{derm}} = \text{TDE} \times \text{DAF} \quad (1)$$

The TDE is calculated in equation (2):

$$\text{TDE} = \sum M_{\text{p},i} \quad (2)$$

where TDE is the total dermal exposure (μg chlorpyrifos), M is the mass (μg) of chlorpyrifos measured for each body part i . Measured body parts included the head, neck, arms, legs, hands and torso. Exposure to hands was measured using handwash techniques. A penetration factor of one was applied for the head and neck since no clothing was worn on these body parts.

The exposure-derived absorbed inhalation dose (EDAD_{inh}) was estimated from equation (3). A 100% absorption factor (AF) was assumed for workers not wearing respiratory protection, whereas a 10% AF was applied to estimates for workers wearing respiratory protection (CFR, 2003). An inhalation rate of 1.5 m^3/h was assumed for all workers

Table 1. Key elements of registrant studies

Reference ^a	n	Job class	Trade name (% chlorpyrifos)	Sampling duration (min)	PPE	Mean pounds of chlorpyrifos handled	Chlorpyrifos formulation type	Application type
Barnekow <i>et al.</i> (1998)	5 ^b	ML/A	Dursban-TC (43.9%)	300–543	Coveralls, gloves ^c , apron ^c , respirator ^c	6.8	Liquid concentrate	Handheld spraygun
Knuteson <i>et al.</i> (1999)	15	ML	Lorsban-4E (45%)	40–131	Coveralls, gloves	411.3	Liquid concentrate	Aerial application
Murphy <i>et al.</i> (1998)	16	ML/A	Lorsban-15G (15%)	104–482	Coveralls	77.8	Granular	Planter
Contardi <i>et al.</i> (1993)	16	ML/A	Empire-20 (20%)	66–107	Coveralls, gloves, respirator, raingear	0.41	Liquid concentrate	Handheld spraygun
Shurdut <i>et al.</i> (1993)	9	ML	Lorsban-4E (50%)	30–318	Coveralls, gloves, respirator, goggles	57.5	Powder/concentrate	Ground boom
	9	A	Lorsban-50W (50%)	30–318	Coveralls	57.5	Wettable powder	Ground boom
	10	RS	NA ^d	30–318	Short-sleeve coveralls	NA ^d	Wettable powder	N/A ^d

^aYear study submitted to EPA.^bA total of 15 workers were monitored for this study. Only five of these workers included biomonitoring as well as WBD methods and thus were used in this analysis.^cSometimes.^dN/A = not applicable.

(USEPA, 1997).

$$EDAD_{inh} = C \times IR \times ED \times AF \quad (3)$$

where $EDAD_{inh}$ is the worker's exposure-derived absorbed inhalation dose (μg chlorpyrifos), C is the measured breathing zone air concentration of chlorpyrifos ($\mu\text{g}/\text{m}^3$), IR is the worker's estimated inhalation rate (m^3/h), and ED is the exposure duration (h).

The total exposure-derived absorbed dose ($EDAD_{tot}$) (μg chlorpyrifos) from passive dosimetry was calculated by summing the $EDAD_{derm}$ (μg chlorpyrifos) and the $EDAD_{inh}$ (μg chlorpyrifos) per equation (4), where each of the variables is as previously defined.

$$EDAD_{tot} = EDAD_{derm} + EDAD_{inh} \quad (4)$$

Biological monitoring of the primary chlorpyrifos urinary metabolite 3,5,6-trichloro-2-pyridinol (3,5,6-TCP) was also used to measure the absorbed dose of chlorpyrifos. The biological monitoring was conducted concurrently with the passive dosimetry. Workers were asked to avoid exposure to chlorpyrifos approximately seven to ten days prior to the exposure and urine collection period. In several instances, surrogate workers ($n = 16$) who performed the tasks of the agricultural worker were monitored instead of actual workers due to difficulties with limiting worker exposure for the required seven to ten day pre-sampling clearance period. Urine samples were collected one day prior to exposure (background), the day of exposure, and four days following exposure. Cumulative urine collected over each twelve-h interval was pooled into one sample for analysis. Laboratory analysis was conducted according to methods described by Bartels and Kastl (1992). In brief, this method consisted of acid hydrolysis, liquid extraction (toluene), and derivitization with *N*-methyl-bis-(tert-butyldimethylsilyl)-trifluoroacetamide (MTBSTFA). The derivitized extract was quantified with negative ion gas chromatography/mass spectrometry (GC/MS) using response factors given from internal standards.

Biomarker-derived absorbed dose (BDAD) was calculated in the same manner in all five studies. Total 3,5,6-TCP excreted was corrected for background exposure, divided by a unitless urinary excretion factor (UEF) of 0.72, and then multiplied by the ratio of the molecular weight of chlorpyrifos (350.6 g/mol) to 3,5,6-TCP (198 g/mol) per equation (5). The UEF was derived from human kinetic data and represents the fraction of an oral dose excreted in urine (Nolan *et al.*, 1984).

$$BDAD = \frac{TCP_A}{UEF \times MW_{TCP}/MW_{Chlor}} \quad (5)$$

where BDAD is the biomarker-derived absorbed dose (μg chlorpyrifos), TCP_A is the application-related mass (i.e. corrected for background) of TCP eliminated in urine. MW_{TCP} and MW_{Chlor} are the molecular weights of 3,5,6-TCP and chlorpyrifos (g/mol), respectively.

In our analysis, the raw data from the studies were analyzed using Intercooled Stata® v8.0. The dermal, inhalation, and biomonitoring variables were found to be non-normally distributed by the Shapiro-Wilk test. Therefore, to assess the relative contribution of dermal and inhalation routes to total exposure and to compare exposure and dose across job class, non-parametric methods were used. The relative contribution of $EDAD_{inh}$ and $EDAD_{derm}$ to predicted $EDAD_{tot}$ was examined using the Wilcoxon Sign-Rank Test. The Wilcoxon Rank-Sum Test was performed to compare $EDAD_{inh}$, $EDAD_{derm}$ and BDAD across job categories. To evaluate the relationship between passive dosimetry results and biomonitoring levels and to identify significant predictors of absorbed dose, simple and multiple linear regression analyses were conducted. BDAD was log-transformed to meet the assumption of normality in the dependent variable.

RESULTS

Across the five registrant studies, there was a total of 80 workers monitored representing a range of formulations, applications, and use of personal protective equipment (PPE) as summarized in Table 1. Inhalation data were missing for three workers, therefore any analyses involving inhalation values included 77 workers.

The distributions of $EDAD_{inh}$ (assuming 100% absorption and 10% absorption for workers wearing respirators) ($n = 77$) and $EDAD_{derm}$ (assuming a 3% DAF) ($n = 80$) by job class are shown in Fig. 1. $EDAD_{inh}$ spanned six orders of magnitude, ranging from 0.064 to 32 400 $\mu\text{g}/\text{day}$. Based on a test of medians, inhalation doses among the job classes were found to be different ($P = 0.02$). Applicators tended to be most highly exposed (median of 74 $\mu\text{g}/\text{day}$, $n = 9$) followed by M/L ($n = 21$), M/L/A ($n = 37$) and RS ($n = 10$) with median values of 44, 30, and 20 $\mu\text{g}/\text{day}$, respectively. Specific differences between job classes were examined using the Wilcoxon Rank-Sum Test, revealing A to be more highly exposed by inhalation relative to RS ($P = 0.03$).

Based on EPA's guidance and evidence by Nolan *et al.* (1984), we assumed a 3% DAF to calculate potential dermal chlorpyrifos dose (USEPA, 1998). $EDAD_{derm}$ estimates assuming 3% DAF ranged from 0.77 to 2340 $\mu\text{g}/\text{day}$. As with inhalation, the difference in $EDAD_{derm}$ among job classes was significant

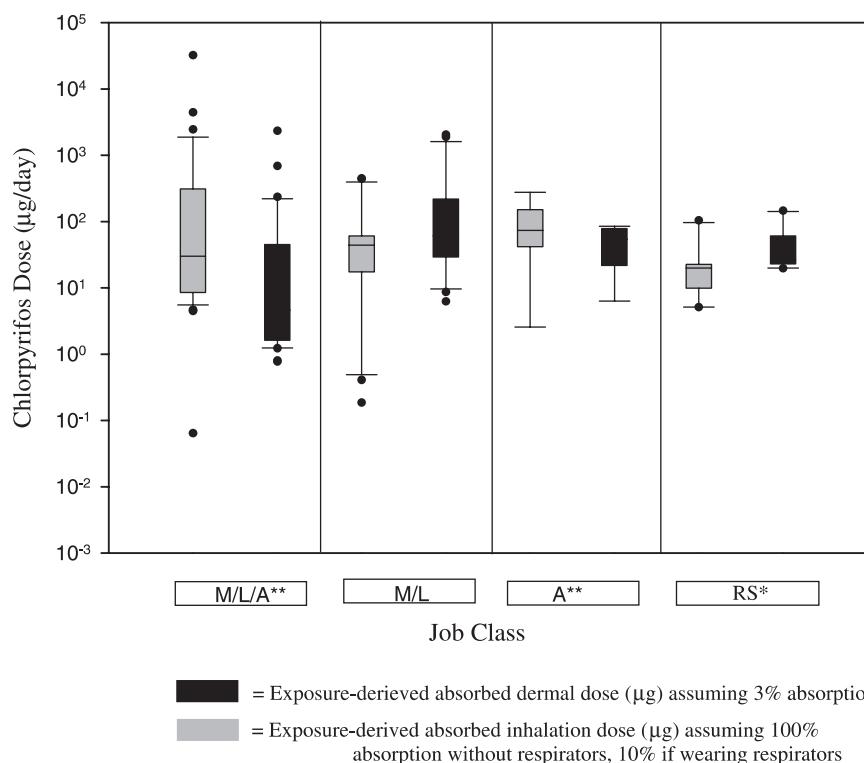


Fig. 1. Distribution of EDAD_{derm} and EDAD_{inh} by job class. *EDAD_{derm} higher than EDAD_{inh} ($n = 10$, $P = 0.005$); **EDAD_{inh} higher than EDAD_{derm} (M/L/A: $n = 37$, $P = 0.03$; A: $n = 9$, $P = 0.03$).

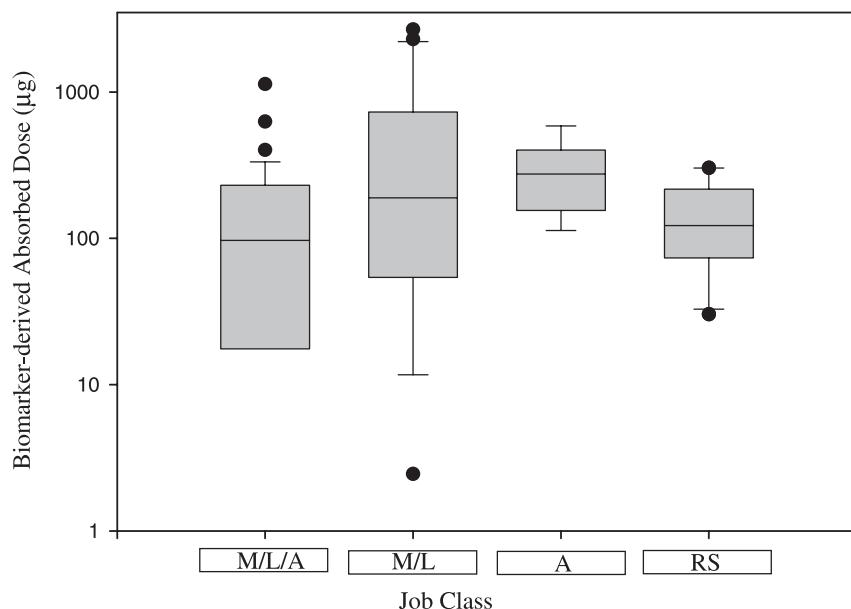
(median test; $P = 0.001$). The Wilcoxon Rank-Sum Test revealed M/L ($P = 0.0001$, $n = 21$), A ($P = 0.027$, $n = 9$), and RS ($P = 0.024$, $n = 10$) were all more highly exposed relative to M/L/A ($n = 37$).

The comparison of EDAD_{derm} to EDAD_{inh} (assuming 3% dermal and 100% or 10% inhalation absorption) provides an indication of their relative contribution (Fig. 1). The Wilcoxon Sign-Rank Test showed that EDAD_{inh} was higher than EDAD_{derm} for two job classes: M/L/A ($n = 37$, $P = 0.03$), A ($n = 9$, $P = 0.03$). In contrast, dermal exceeded inhalation dose for RS ($n = 10$, $P = 0.005$). The relative dose contribution was examined as the ratio (EDAD_{derm}:EDAD_{inh}) by job class (Table 2). Re-entry scouts had the highest median ratio of 1.66 while M/L/A had the lowest ratio of 0.17, with an overall median ratio across the four job categories of 0.49. Ratios were highly skewed (especially M/L) as indicated by a large difference between mean and median values. In 34 of 77 workers (44%) the ratio exceeded one indicating that dermal exposure dominated inhalation.

EDAD_{tot} (assuming 3% dermal and 100% inhalation absorption if no respiratory protection worn and

10% if a respirator worn) ranged from 5.5 to 32 445 µg/day with A most highly exposed (median 129 µg/day) followed by M/L/A, M/L and RS, with median values of 88, 85 and 45 µg/day, respectively ($n = 77$). Significant differences in EDAD_{tot} by job class were not detected in a global median test ($P = 0.18$). However, the Wilcoxon Rank-Sum Test revealed statistically significantly higher EDAD_{tot} levels in M/L relative to RS ($P = 0.007$).

The variability in exposure by method of application (planters, handheld sprayers, aerial sprayers and ground boom) was also examined (see Table 3). Workers performing ground boom applications had the highest median EDAD_{derm} of 82.7 µg/event ($n = 18$), followed by aerial applications (39.0 µg/event, $n = 15$), handheld spraying applications (33.0 µg/event, $n = 21$) and planter applications (1.9 µg/event, $n = 16$). A global median test evaluating the differences in EDAD_{derm} by application type yielded a P -value of < 0.001 . Specifically, planters were less than handheld sprayers ($P = 0.0001$), aerial sprayers ($P < 0.0001$) and ground boom applicators ($P < 0.0001$). The difference between handheld



M/L/A =Mixer/Loader/Applicator
 M/L = Mixer/Loader
 A = Applicator
 RS = Re-entry Scout

Fig. 2. Distribution of BDAD by job class. Wilcoxon Rank-Sum Test for differences between job classes: (A) M/L/A and M/L, $P = 0.04$; (B) M/L/A and APPL, $P = 0.02$; (C) M/L/A and RS, $P = 0.5$; (D) M/L and APPL, $P = 0.6$; (E) A and RS, $P = 0.06$; (F) M/L and RS, $P = 0.57$.

Table 2. Distribution of ratio of EDAD_{derm}^a to EDAD_{inh}^b (µg/application) by job class

	M/L/A	M/L	A	RS	Overall
<i>n</i>	37	21	9	10	77
5%	0.001	0.23	0.19	1.08	0.003
25%	0.01	0.49	0.31	1.32	0.18
50%	0.17	1.55	0.43	1.66	0.49
Mean	2.11	135	1.69	2.57	38.5
75%	0.47	3.16	0.66	3.63	2.27
95%	21.4	501	11.2	6.54	21.4

Sample size = 77 (inhalation data unavailable for three workers).

^aAssumes 3% dermal absorption.

^bAssumes 100% inhalation absorption, 10% if respirator worn.

Table 3. Median EDAD_{inh}^a and EDAD_{derm}^b by application type (µg/application)

Application type	EDAD _{inh}	EDAD _{derm}	EDAD _{tot} ^c
Planter	8.5	1.9	11
Aerial sprayer	44	39	78
Ground boom	74	83	202
Handheld sprayer	76	33	418

^aAssumes 100% inhalation absorption, 10% if respirator worn.

^bAssumes 3% dermal absorption.

^cDetermined from equation (4).

Wilcoxon Rank-Sum Test for differences between groups (only differences with $P < 0.05$ shown): inhalation: (A) planter and aerial, $P = 0.003$; (B) planter and handheld, $P = 0.0003$; (C) aerial and handheld, $P = 0.04$; dermal: (D) planter and handheld, $P = 0.0001$; (E) planter and aerial, $P < 0.0001$; (F) planter and groundboom, $P < 0.0001$.

spray and ground boom applicators was marginal ($P = 0.055$), as was the difference between aerial spray and ground boom ($P = 0.06$).

The EDAD_{inh} distribution by method of application differed from EDAD_{derm}. For EDAD_{inh}, handheld sprayers had the highest median level followed by ground boom, aerial sprayer and planters. As with EDAD_{derm}, planters EDAD_{inh} was less than handheld sprayers ($P = 0.0003$), aerial sprayers ($P = 0.003$) and, marginally, groundboom applications ($P = 0.06$). Furthermore, EDAD_{inh} by handheld spraying was greater than aerial spraying ($P = 0.04$).

The chlorpyrifos BDAD estimated from urinary 3,5,6-TCP ranged from -87 to 2681 µg/day (negative values indicate higher pre-application levels

relative to post-application), with a median of 163 µg/day ($n = 80$). Applicators had the highest median BDAD (275 µg/application), followed by M/L, RS and M/L/A, with median dose values of 189, 122 and 97 µg/application, respectively (Fig. 2). Differences in BDAD by job class were not statistically significant in a global median test ($P = 0.24$). However, results of the Wilcoxon Rank-Sum Test revealed that M/L had statistically significantly higher absorbed dose levels than M/L/A ($P = 0.04$), and A had higher dose levels than M/L/A ($P = 0.02$). Applicator BDAD levels were marginally significantly higher relative to RS ($P = 0.06$).

EDAD_{tot} estimated from external passive dosimetry assuming three DAFs (1, 3 and 10%) was compared with BDAD. Ratios of the external estimates to the biomarker values by job classification revealed that a 3% dermal absorption factor (DAF), the EPA's accepted DAF, resulted in a median ratio of 0.71, as compared with a 1% DAF (median ratio = 0.45) and 10% DAF (median ratio = 1.28) (Fig. 3).

Regression analysis was used to examine determinants of BDAD considering independent variables, including: (i) EDAD_{inh} (assuming 100% and 10% AF for workers without and with respirators, respectively); (ii) EDAD_{derm} (assuming 3% DAF, including and excluding hands and hands by themselves); (iii) EDAD_{tot}; (iv) formulation type; (v) pounds of pesticide handled; (vi) application type; (vii) job class; (viii) personal protective equipment (PPE) type; (ix) sample duration; (x) bodyweight; and (xi) % formulation. BDAD was log-transformed due to its skewed distribution. EDAD_{tot} explained 29% of the variability in BDAD from simple linear regression analysis (Fig. 4). A more complex multivariate regression model was considered to explain additional variability. Both the inhalation and dermal doses were included *a priori*. In order to be considered for inclusion in the multivariate model, the additional variables needed to achieve a P -value of <0.2 in the simple linear regression model (Table 4). Variables satisfying this criterion included: pounds chlorpyrifos handled, application type, % chlorpyrifos formulation, PPE type, job type, formulation type and sample duration.

The multiple linear regression model was built in a stepwise fashion using the variables identified as potentially important from the simple linear regression results. Due to the suspected correlation among some of the independent variables (e.g. application type and PPE use), several different models were developed with different combinations and ordering of variables. Interaction among variables was also explored. We selected the variables for the final model based on the following criteria: statistical significance, strength of association, parsimony, and the amount of variability explained by the model (R^2). This model (equation 6) includes the variables

EDAD_{derm}, EDAD_{inh}, and application type (i.e. hand-wand, groundboom, aerial or corn planter). The application type variables were treated as indicator variables in our model, with corn planters serving as the reference group. In this final model, EDAD_{derm} was marginally statistically significant ($P = 0.066$) whereas EDAD_{inh} was not ($P = 0.59$). The regression coefficient for EDAD_{derm} (0.0007) exceeded EDAD_{inh} (0.00002) by a factor of 35. Overall, the final model included a total of three independent variables (including the two dose variables) and explained 46% of the variability in the log-transformed urinary 3,5,6-TCP (BDAD) ($n = 62$) (Table 4). The RS were dropped from this regression model because they could not be assigned to an application type, as well as five workers missing 3,5,6-TCP data, and three workers missing inhalation data.

$$\ln(TCP) = \beta_0 + \beta_1(EDAD_{derm}) + \beta_2(EDAD_{inh}) \\ + \beta_3(App_{HS}) + \beta_4(App_{AS}) \\ + \beta_5(App_{GB}) + \varepsilon_i \quad (6)$$

where $\ln(TCP)$ is the natural log of the 3,5,6-TCP mass eliminated in urine (µg), β_0 is the intercept, β_n are the variable coefficients, EDAD_{derm} and EDAD_{inh} are as previously defined, App_{HS}, App_{AS} and App_{GB} are indicator variables for pesticide application by handheld sprayer, aerial sprayer and ground boom, respectively, and ε_i is the model error.

DISCUSSION AND CONCLUSIONS

Exposure assessment is crucial to evaluating the hazard posed to agricultural pesticide handlers. The current study provides such an assessment across a range of studies and job classes. Exposure has been assessed based both on external measurements and biological monitoring, affording the opportunity to not only evaluate the relative routes of exposure but also to examine the predictive association between the two methods of assessment. Exposure was examined by job class as suggested by Henderson *et al.* (1993).

Among the four job classes investigated, A were consistently ranked as the most highly exposed based on median values of both EDAD_{tot} and BDAD. This finding agrees with Cattani *et al.* (2001), who attributed higher exposures among pesticide applicators to frequent spills on the body and improper use and poor condition of PPE. Applicators also had the highest median EDAD_{inh} consistent with the aerosolization required for application. This finding is in contrast with Krieger (1995) who suggested that M/L/A have the highest exposure potential. However, in the current study, six of the 33 M/L/A wore

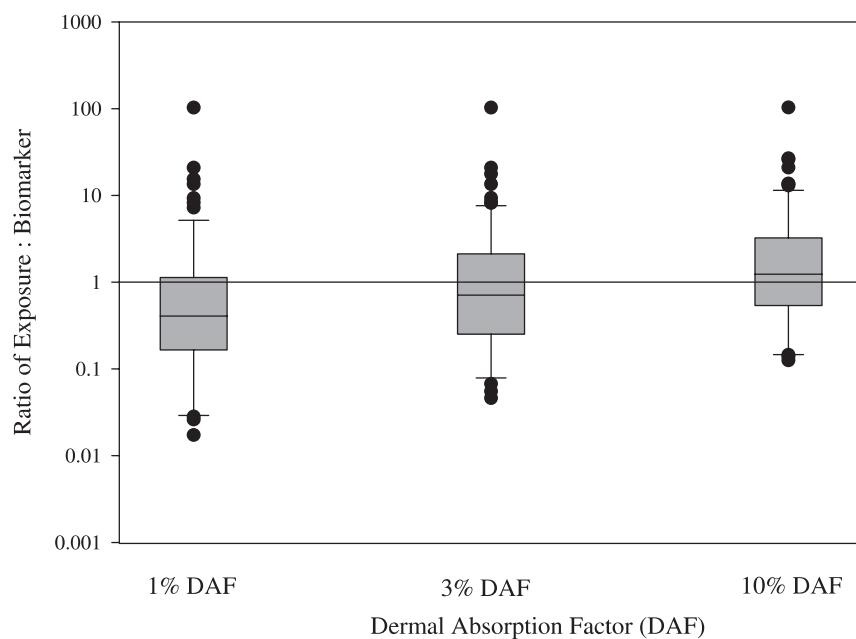
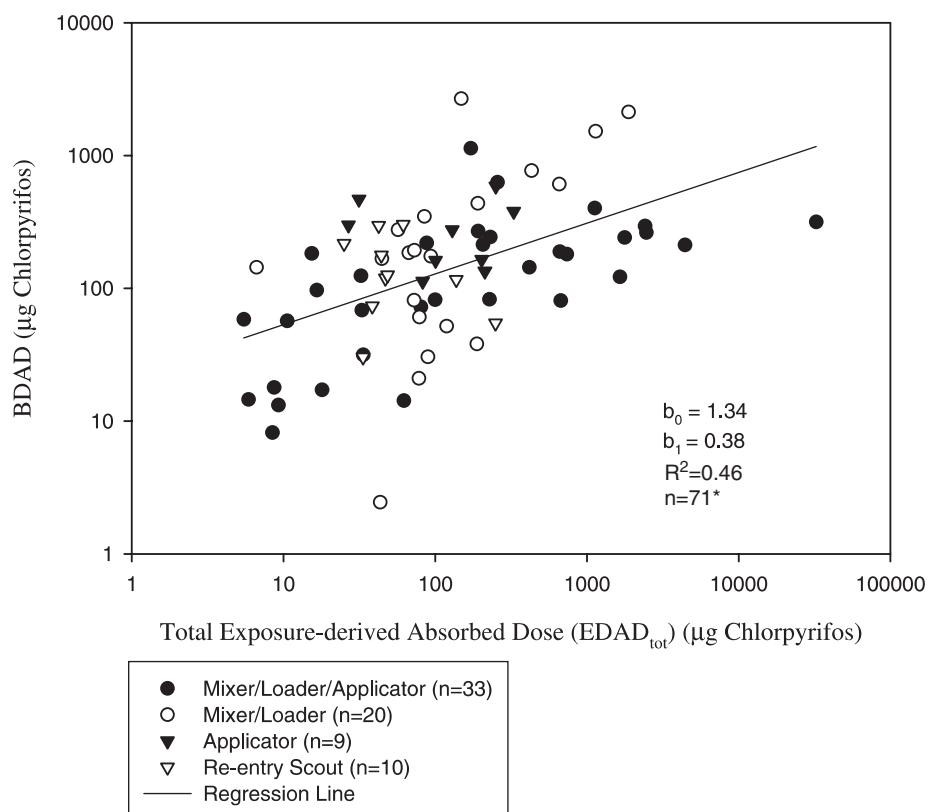


Fig. 3. Ratio of EDAD_{tot} and BDAD by dermal absorption factor ($n = 77$; inhalation data unavailable for three workers).



*Excludes three workers whose inhalation exposure was not measured and five workers with a negative BDAD after background correction.

EDAD_{tot} is based on 3% absorption factor for dermal exposure and a 100% absorption factor for inhalation exposure (10% with respirator).

EDAD_{tot} and BDAD are as defined in Equation 4 and 5, respectively (unadjusted for body weight).

Fig. 4. Regression of BDAD on EDAD_{tot}.

Table 4. Simple linear regression results where log BDAD (μg) is the dependent variable

Independent variable	Regression coefficient	Standard error	95% confidence interval	P-value	R^2
EDAD _{inh} ^a (μg)	0.000034	0.000039	(-0.000045, 0.00011)	0.39	0.01
EDAD _{derm} ^b (μg)	0.0012	0.00032	(0.00062, 0.0019)	<0.001	0.18
EDAD _{derm} excluding hands ^b (μg)	0.0012	0.00032	(0.00059, 0.0019)	<0.001	0.17
EDAD _{derm} to hands only ^b (μg)	0.021	0.0069	(0.007, 0.035)	0.004	0.11
Bodyweight (kg)	-0.005	0.0085	(-0.022, 0.011)	0.51	0.006
Percent formulation	0.02	0.01	(-0.0081, 0.05)	0.15	0.045
Pounds handled	-0.0014	0.00099	(-0.0034, 0.00057)	0.16	0.031
Sample duration	-0.0016	0.0012	(-0.0041, 0.00087)	0.20	0.02
Job code ^c					0.08
M/L	0.71	0.35	(0.21, 1.42)	0.044	
A	0.87	0.48	(-0.093, 1.84)	0.076	
RS	0.17	0.46	(-0.76, 1.09)	0.72	
Formulation type ^d					0.30
Granular	-1.82	0.37	(-2.55, -1.08)	<0.001	
Wettable powder	0.27	0.29	(-0.31, 0.86)	0.36	
PPE type ^e					0.22
Coveralls, gloves	0.79	0.41	(-0.028, 1.61)	0.058	
Coveralls, gloves, respirator	1.41	0.32	(0.78, 2.04)	<0.001	
Application type ^f					0.45
Handheld sprayer	1.98	0.38	(1.21, 2.74)	<0.001	
Aerial application	1.23	0.41	(0.40, 2.05)	0.004	
Ground boom	2.64	0.39	(1.86, 3.42)	<0.001	

^a Assumes 100% inhalation absorption without respirator, 10% if wearing respirator.

^b Assumes 3% dermal absorption.

^cCategorical variable using M/L/A as reference group.

^dCategorical variable using liquid concentration as reference group.

^eCategorical variable using 'coveralls only' as reference group.

^fCategorical variable using planter as reference group.

respirators thereby decreasing their exposure potential, whereas none of the A wore respirators.

The BDAD rank across the remaining job classes was M/L > RS > M/L/A whereas the EDAD_{tot} was M/L/A > ML > RS. Median EDAD_{inh} and EDAD_{tot} ranked the lowest for RS consistent with their job function that excludes working with the aerosolized pesticide. For this group, both BDAD and EDAD_{derm} were similarly ranked as third highest, suggesting that the dermal methods underlying EDAD_{derm} were effective in classifying these workers whose exposure was likely dermal dominated. M/L/A were inconsistently ranked as second and fourth by BDAD and EDAD_{tot}, although EDAD_{derm} was consistent with BDAD (fourth), suggesting that inhalation exposure was potentially overestimated for this class.

Dermal exposure by itself tended to be highest among M/L, where there is risk for hand exposure to concentrated solutions. The high dermal exposure in this group was driven by extreme values among a small number of workers (shown in Fig. 1 and Table 2) implicating work practices as an exposure determinant. Machado-Neto and Matuo (1998) and Chester (1993) observed that 86% of exposure to M/L was to the hands. The significance of dermal exposure

across all job classes was substantiated based on exposure measurements (i.e. EDAD_{derm} assuming 3% absorption and EDAD_{inh} assuming 100% absorption) identifying a median dermal to inhalation ratio of 0.6. This ratio exceeded unity for 34 of 77 workers (44%) indicating that the dermal exposure pathway was dominant for nearly half of all workers.

Variability occurring within and among studies could be due in part to differences in the application device, PPE use, spray technique, and quantity and formulation of pesticide applied. For example, the current study showed that among application types, workers applying chlorpyrifos by ground boom received higher dermal exposures relative to aerial, handheld sprayers or planters. The highest median inhalation exposure occurred among handheld sprayers (76 $\mu\text{g}/\text{application}$) although ground boom applicators were a close second (74 $\mu\text{g}/\text{application}$). Total exposure was greatest among handheld sprayers with a median of 418 $\mu\text{g}/\text{application}$, exceeding ground boom (202 $\mu\text{g}/\text{application}$), aerial sprayer (78 $\mu\text{g}/\text{application}$) and planter (11 $\mu\text{g}/\text{application}$) by factors of 2.1, 5.4 and 38. Rutz and Krieger (1992) examined exposure levels in 19 groups of pesticide M/L and A in California and found that

Table 5. Covariates in final multiple linear regression model with log-transformed 3,5,6-TCP, the BDAD (μg), as dependent variable ($R^2 = 0.46$; $n = 62$)

Independent variables	Regression coefficient	Standard error	95% confidence interval	P-value
EDAD _{derm} ^a (μg)	0.0006	0.00035	(-0.00004, 0.0014)	0.066
EDAD _{inh} ^b (μg)	0.000019	0.00003	(-0.00004, 0.00008)	0.57
Application type ^c				
Handheld sprayer	1.18	0.39	(1.03, 2.59)	<0.001
Aerial application	1.2	0.41	(0.38, 2.02)	0.005
Ground boom	2.32	0.41	(1.49, 3.13)	<0.001
Intercept	3.37	0.29	(2.78, 3.97)	<0.001

^a Assumes 3% dermal absorption.

^b Assumes 100% inhalation absorption without respirators, 10% if wearing respirator.

^c Categorical variable using planter as reference group.

application with a hand wand accounted for the highest exposure levels (1040 $\mu\text{g}/\text{h}$) in comparison to application with a ground boom or aerial application. They also found that M/L involved in open dumping of powder formulations received the highest mean exposure (24 274 $\mu\text{g}/\text{h}$). Attempts at lowering worker exposure potential in packaging have included the use of dripless containers, integrated handling systems and other mechanical transfer systems, as well as enclosure of work processes. Thus formulation, application type and product packaging may serve as useful indicators of worker exposure.

The DAF was examined by comparing (as a ratio) the absorbed dose estimated from exposure (EDAD_{tot}) and biomarker measurements (BDAD). This ratio was evaluated across three assumptions of DAF (i.e. 1, 3 and 10%). A study by Nolan *et al.* (1984) supports the use of a 3% DAF, the EPA's accepted value, whereas Krieger (1995) supports a 10% DAF and Griffin *et al.* (1999) report a 1% DAF. Our findings suggest that the DAF lies in the range of 3–10%.

Using a multiple linear regression model, 46% of the variability in the urinary 3,5,6-TCP levels could be explained. The unexplained variability may stem from measurement error in the dependent or independent variables or misalignment in timing in collection of biomarker samples relative to exposure. The dermal exposure estimate is especially vulnerable to error because of the assumptions required including that the dosimeter has retention similar to the skin and that dermal absorption is a constant. Cross-contamination can also occur during dosimeter removal. Thus, dermal exposure estimates may be more prone to uncertainty due to difficulty in standardization of the method and error associated with assumptions of the method. Woollen (1993) suggests that a nonlinear relationship between external exposure estimates and biomonitoring exists due to factors such as differences in personal hygiene habits (i.e. washing) and individual differences in metabolism. The rate of pesticide metabolism in the worker

is influenced by duration and rate of exposure. The absorption process is thought to be saturable, not conforming to a linear dose-response model (Zendzian, 2000). Others suggest that the variability seen in passive dosimetry estimates might be attributable to lack of standardization of methods and exclusion of the ingestion pathway.

Fenske and Elkner (1990) identified similar positive associations of the 3,5,6-TCP urinary metabolite and external exposure measures ($R^2 = 0.86$) in a study of residential pesticide applicators. Hines and Deddens (2001) found positively and highly correlated weekly means of ln(TCP) and ln(chlorpyrifos air concentrations) ($R^2 = 0.73$, $P < 0.0001$) in 41 termiticide applicators in North Carolina. In an environmental in-home exposure assessment, Buckley *et al.* (1997) found that 3,5,6-TCP levels in the urine were moderately correlated with indoor air ($R^2 = 0.55$; $P \leq 0.01$) and dust ($R^2 = 0.46$; $P \leq 0.01$) concentrations of chlorpyrifos during two seasons of sampling.

The fact that dermal exposure represents a substantial portion of pesticide workers' exposure and yet there are no standard methods of assessment, highlights a significant gap in the protection of worker health and safety. For some chemicals, this gap is addressed through biological-based exposure indices (e.g. ACGIH Biological Exposure Indices or BEIs[®]), however, such an index is not available for chlorpyrifos exposure other than nonspecific cholinesterase inhibition [American Conference of Governmental Industrial Hygienists (ACGIH, 2001)], which was unmeasured in the current study. The inhalation 8 h Threshold Limit Value (TLV[®]) (ACGIH, 2001) of 0.2 mg/m³ was exceeded for two M/L who had 8 h time-weighted averages of 0.37 mg/m³ (assuming no exposure for the balance of the workday). However, both workers wore respirators so that the measured air concentration was not representative of their inhalation exposure. Study results are compared with the 2001 rather than the current TLV[®] because the current guideline is based on inhalable sampling

whereas the earlier TLV[®] was consistent with methods used in the registrant studies, i.e. 37 mm filter cassettes.

There are study caveats and/or limitations associated with the use of registrant studies to be considered in interpreting the current results. The use of WBD to measure dermal exposure alters (reduces) the amount of chlorpyrifos absorbed thereby affecting urinary TCP levels. Therefore, BDAD will underestimate exposure relative to what would occur without WBD monitoring. To the extent that BDAD is underestimated, the DAF derived from the ratio of EDAD_{total} to BDAD will be overestimated and the slope of BDAD regressed EDAD will be underestimated. Another limitation relates to the reliance on secondary data. It is significant to note that despite the added protection afforded by the WBD, 75 out of 80 workers had measurable levels of urinary 3,5,6-TCP associated with chlorpyrifos application. Although all studies used a common set of methodological guidelines designed to minimize measurement differences across studies (USEPA, 1998), each study was conducted independently and it is possible that there were subtle methodological differences in sampling and/or analysis that resulted in an unknown bias.

Overall, the EPA's Pesticide Registrant Database provided useful information for evaluating pesticide worker exposure and worker exposure assessment methods. These data help demonstrate the significance of the dermal route of exposure in pesticide workers. This analysis also served to demonstrate the public health utility of the EPA's Pesticide Registrant Database. This untapped resource should be made publicly available for the purpose of evaluating exposure assessment methods to better protect worker health.

This study highlights the need for continued development of methods to assess worker dermal exposure in the workplace to close the unexplained variability gap between measures of exposure and biological monitoring.

Disclaimer—This paper has been reviewed in accordance with the US Environmental Protection Agency's peer and administrative review policies and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

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