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Pilot biomonitoring of adults and children following use of chlorpyrifos shampoo and flea collars on dogs

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Pesticide handlers and pet owners who use products such as shampoos and dips and insecticide-impregnated collars to treat and control fleas on companion animals are exposed to a variety of active ingredients. Chlorpyrifos exposures of adults and children were measured using urine biomonitoring following use of over-the-counter products on dogs. Age and gender-specific measurements of urinary 3, 5, 6-trichloro-2-pyridinol (TCPy) revealed modest elevations of biomarker excretion following shampoo/dips. Smaller TCPy increments were measured following application of impregnated dog collars. The extent of indoor activity and potential pet contact were important determinants of urine biomarker level. Children without direct pet contact excreted more TCPy following collar application. Pet collars may be a source of indoor surface contamination and human exposure. Children excreted up to 4 times more TCPy than adults when urine volumes were adjusted using age-specific creatinine excretion levels. Although chlorpyrifos is no longer used in the United States in pet care products, results of this research provide perspective on the extent of human exposure from similar pet care products. These pilot studies demonstrated that pet care products such as insecticidal shampoos and dips and impregnated collars may expose family members to low levels of insecticide relative to toxic levels of concern.

Keywords: Chlorpyrifos; biomonitoring; human exposure; pet care insecticide; children; insecticide.

Introduction

Insecticides are extensively used by the public and professionals for the treatment and control of fleas, ticks and other pests on companion animals. Sprays, powders, dusts, shampoos, collars, and spot-on treatments for dogs and cats contain a variety of active ingredients.

Very limited human exposure data representing the use of pet care products are available for aggregate exposure assessments for pesticide handlers and pet owners. The human exposure potential of pet care products is defined by limited published reports referring to personal and occupational exposure.[1–6] Generally, these investigators have estimated the availability of residues by measuring residues removed by petting dogs with absorbent cotton gloves (Fig. 1). The results show that insecticide residues persist and are transferable to gloves for variable periods, but the glove method to estimate dose for human exposure and risk assessment has not been validated.

Chlorpyrifos, the leading organophosphorous insecticide in agriculture,[7] was formerly the most extensively used residential pest management insecticide prior to 1997.[8] At that time negotiations between the USEPA and Dow AgroSciences resulted in the registrant's decision to withdraw support of indoor chlorpyrifos registrations including pet pest treatments. Products remained available in the channels of trade until inventories were exhausted. Some participants in the Personal Chemical Exposure Program research on chlorpyrifos foggers in the 1990's[9] also used pet products containing chlorpyrifos and provided urine specimens for these pilot biomonitoring studies with pet care products. The products are no longer in commerce in the United States.

The exposures of adults and children reported here followed label directions of chlorpyrifos dog shampoos or dips and flea collars that are no longer in commerce. These measurements of 3, 5, 6-trichloro-2-pyridinol (TCPy) chlorpyrifos biomarker in spot urine specimens with age- and gender-specific volume adjustments using creatinine[10] contribute to the limited

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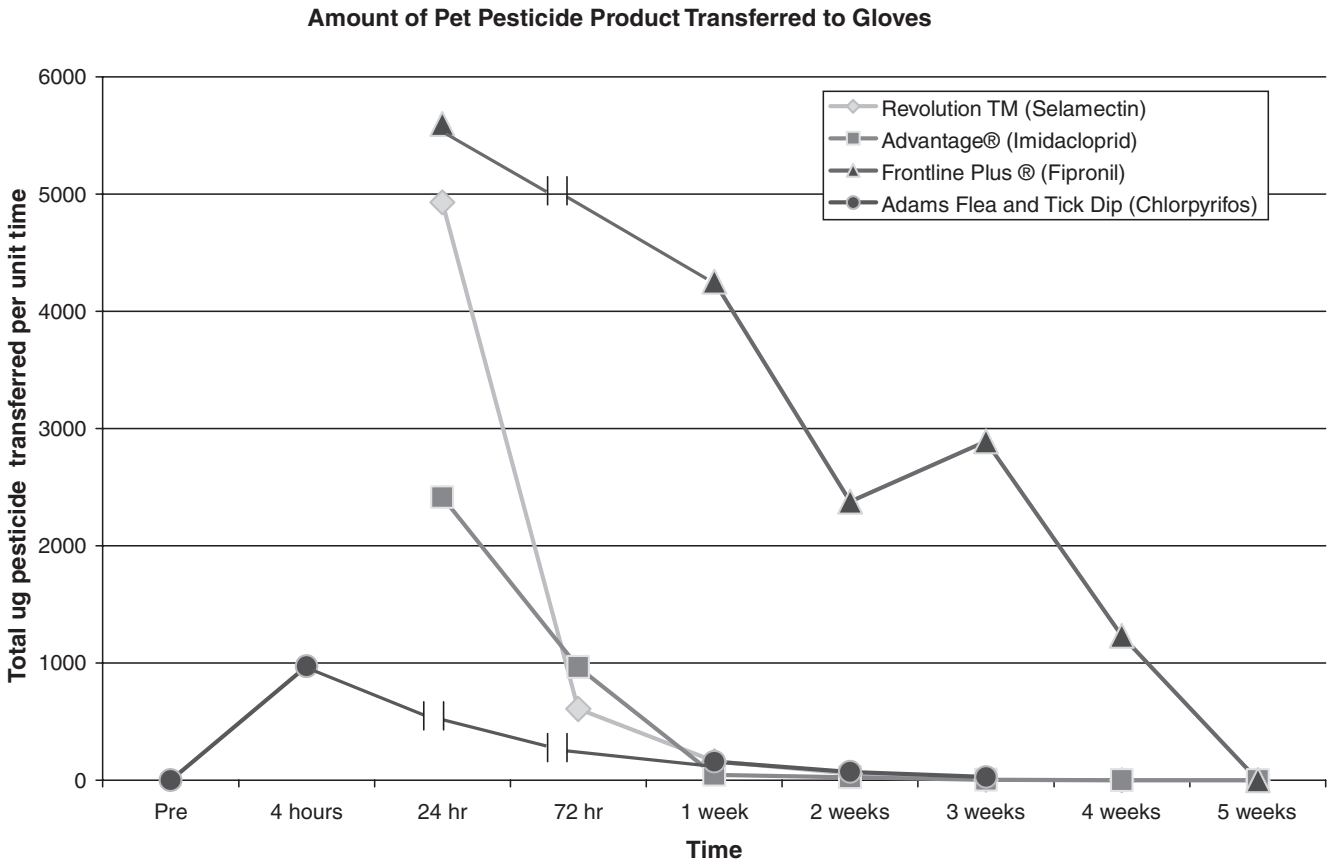

Fig. 1. Potential transferability of pet pest products from dogs indicated by residue on 100 % cotton gloves following 5 min petting. Fipronil,[2] Imidacloprid,[3] and Selemectin [4] data were derived using published data and average glove weight was derived in 2008 a personal communication with R. C. Gupta. Chlorpyrifos data represent four consecutive treatments with flea control dip;[1] other products were applied as spot-on treatments. Reprinted with permission from Driver et al.[6] Copyright 2010 Elsevier/Academic Press.

database of human chlorpyrifos exposures from pet product use.

Methods

Protocol

A protocol for residential pesticide exposure monitoring including informed consent was reviewed and approved by the University of California, Riverside (UCR), Human Subjects Review Committee (now UCR Institutional Review Board). Signed informed consent was obtained from adults who authorized participation of minor children.

Participants

Participants purchased or were given a chlorpyrifos-containing product for treatment and control of fleas during 2000–2003. The products were used as directed on the participant's household pets without supervision except intervention by supply of urine specimen containers, insulated sample carriers, and refreezable coolant (Blue Ice®). Following use of flea products (shampoo, dip or flea collars) pet owners provided serial urine specimens for analysis of the exposure biomarker TCPy. With the exception of family members of the principle investigator, study participants were paid five dollars for each urine specimen contributed to these pilot studies.

Pet Care

Pest management products were purchased in normal channels of trade. In general, the following procedure was followed by study participants. The liquid shampoo or dip was prepared from concentrate (3.84 % w/v chlorpyrifos) at a rate of about 60 mL per gallon. Dogs were thoroughly wetted with warm water and the chlorpyrifos emulsion was swabbed or patted onto the dogs' coat using a washcloth or sponge. Pet owners used about 0.25 to 3.8 L chlorpyrifos emulsion for each dog. Since direct skin contact with the shampoo was short and limited by use of a washcloth or sponge, gloves were not worn. Pet owners applied flea collars (8 % w/w chlorpyrifos) wearing disposable latex or nitrile gloves that were made optionally available by the

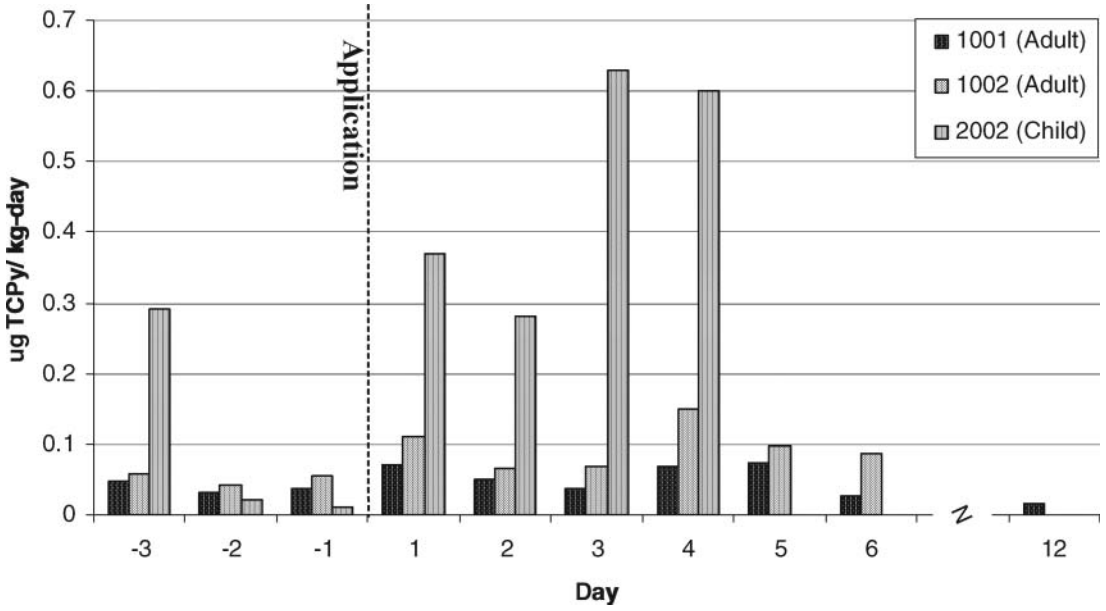

Fig. 2. TCPy excretion in μg chlorpyrifos equivalents per kilogram body weight per day for a family after use of a pet flea shampoo containing chlorpyrifos. The dotted line represents time of application while there is a break between days 6 and 12 in urine sample collection.

study staff to minimize direct skin contact with the flea product. The use of gloves was not a label requirement.

Biomonitoring

Biomonitoring usually began before the dog(s) were treated and continued for three or four days. Urine specimens were collected one, two, and/or three mornings prior to and on the day of the shampoo/dip application or when the flea collar was used. Samples were collected as 25–30 mL specimens of a complete morning void and stored frozen in 30 mL polyethylene tubes prior to analysis.

In order to measure chlorpyrifos exposures, the individual's morning urine samples were analyzed for 3, 5, 6-trichloro-2-pyridinol. TCPy is eliminated primarily in the urine as TCPy-glucuronide with a half-life of approximately 27 hours.[11–13] TCPy concentrations were corrected for volume by creatinine. No corrections were made for control levels of TCPy that were present in all urine specimens.[9] It is important to note that TCPy is a biomarker of both methyl and ethyl chlorpyrifos.[14]

Analysis

All urine specimens were coded and analyzed by chemists blinded to the study objectives. Pacific Toxicology Laboratories (Chatsworth, CA) analyzed conjugated and unconjugated TCPy from acid hydrolysates of urine. The internal standard, $^{13}C_2$ ^{15}N-labeled-TCPy was added to a 5 mL aliquot of thawed urine. Specimens plus 0.25 mL concentrated HCl were held overnight at 60°C. TCPy was extracted with 1-chlorobutane and derivatized in an autosampler vial with *N*-methyl-*N*-(*tert*-butyldimethylsilyl)-trifluoroacetamide reagent to produce *tert*-butyldimethyl derivatives of TCPy and the internal standard. The samples were analyzed by GLC with mass selective detection. Five external calibration blanks covered the range 20 to 200 μg TCPy/L. The limit of quantification for TCPy in urine was 3 to 5 ppb.

Results

Study 1

In June of 2000, a family of three was biomonitored after use of a shampoo/dip on an 11 kg dog without a history of previous treatment with pet care products. The pet owner (1002) who bathed the dog had pretreatment TCPy urine levels of from 0.04 to 0.07 μg TCPy/kg-d and levels of from 0.08 to 0.18 μg TCPy/kg-d during the next 6 days (Fig. 2). TCPy excretion by the 11 year-old child (2002) who had substantial contact with the dog before and after the shampoo ranged from 0.01 to 0.28 μg TCPy/kg-d pre-application and from 0.28 to 0.63 μg TCPy/kg-d after treatment. The head of household (1001) who had little or no contact with the pet, and was out of the home most of the day, showed no increase in biomarker excretion.

Study 2

A second family of four was also monitored in 2000 during a five-day period after use of the chlorpyrifos-containing

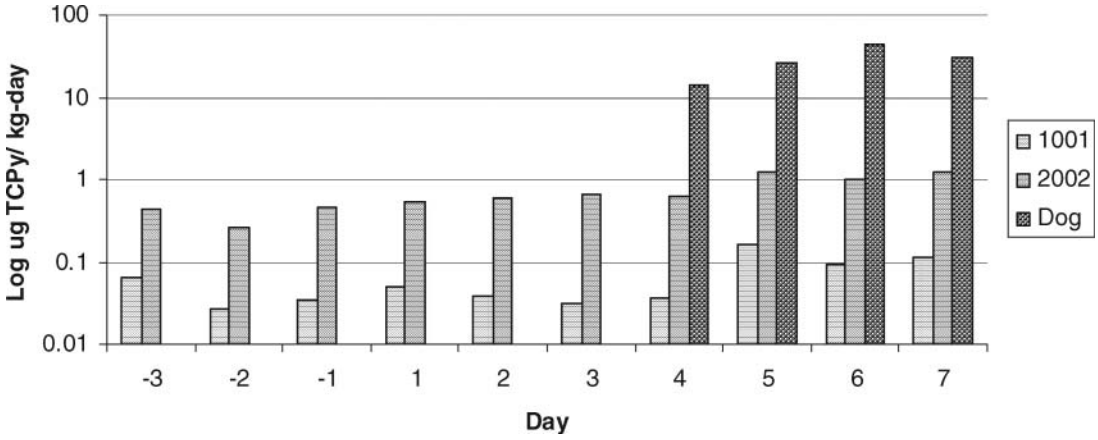

Fig. 3. Chlorpyrifos excretion in μg chlorpyrifos equivalents per kilogram body weight per day for two persons (child 2002 and adult 1001) and their pet dog after use of a dog collar containing 8 % chlorpyrifos.

pet shampoo. Pre-application levels for the family ranged from 0.23 to 1.36 μg TCPy/kg-d while post application levels ranged from 0.23 to 3.92 μg TCPy/kg-d.

Study 1 and Study 2 represent limited time periods and small numbers of persons living in residences with dogs shampooed with the chlorpyrifos product. Figure 2 was selected to demonstrate the importance of activity pattern as a determinant of exposure. The adult (1002) who applied the shampoo/dip and was at home all day with the pet had higher exposure than the head of household (1001) who had little or no pet contact. Both adults had substantially less TCPy excretion than the child during the 4 days of monitoring following the use of the shampoo. Prior to use of the shampoo/dip, urine specimens of all participants contained very low levels of TCPy (as in all urine biomonitoring done by PCEP, unpublished observations).

Study 3

Persons in Study 1 were again biomonitored three years later (May 2003) following use of a flea collar containing chlorpyrifos (Fig. 3). The father, participant 1001, had limited pet contact and did not show a significant increase in TCPy. The pre-collar application TCPy levels ranged from 0.02 to 0.04 μg TCPy/kg-d and post-application urine levels ranged from 0.02 to 0.09 μg TCPy/kg-d. The child (2002) did show slightly increased levels of TCPy excretion above background. Pre-application levels ranged from 0.25 to 0.26 μg TCPy/kg-d and during collar application ranged from 0.30 to 0.70 μg TCPy/kg-d (Fig. 3).

As an adjunct to the human biomonitoring, the dog was also biomonitored. The dog was not biomonitored before application of the pet collar, but post-application urine excretion levels ranged from 3.97 to 12.16 μg TCPy/kg-d (assuming 0.16 g creatinine/d for the 13 kg dog). This extent of excretion was remarkable compared to the levels excreted by the pet owners (Fig. 3). Boone et al.[1] reported cholinesterase inhibition in dogs treated with flea products as a measure of their exposure, but human biomonitoring data were unavailable in that report. Our observations of exposure of the dog (Fig. 3) prompt the suggestion that collar use may have resulted in the transfer of insecticide into the family residence.

Study 4

Interesting and important results were obtained by a Seattle family of two adults (5003 and 5004) and two young children aged 3 (5001) and 5 (5002) years with two small dogs (each < 6 kg). All family members registered TCPy during the 3-day pretreatment period. The residence had no previous use of chlorpyrifos pesticide products, although their previous residence had been fogged about one year earlier. Adult TCPy excretion levels prior to use of chlorpyrifos flea collars ranged from 0.04 to 0.13 μg TCPy/kg-d. During the month-long urine monitoring, the adults excreted from 0.04 to 0.18 μg TCPy/kg-d. An adult was at home with the children throughout the day. While no residential monitoring was performed, increased TCPy excretion in the children after application of a pet collar is likely indicative of a residential exposure since the children had no known direct contact with the dogs. At this stage of their lives, the young children avoided all direct contact with the dogs that were relatively new to the family, although they both spent their days indoors. The children's TCPy excretion levels remained elevated throughout the monitoring period (Fig. 4). The child to adult TCPy ratio was about 4:1 during the control and post-application periods. The adults averaged 0.07 μg TCPy/kg-d pretreatment and 0.09 μg TCPy/kg-d post treatment while the children averaged 0.28 μg TCPy/kg-day pretreatment and 0.39 μg TCPy/kg-d post treatment.

Since there was no known direct contact with the collared dogs, we conclude that the dogs' flea collars introduced available chlorpyrifos or TCPy residue into the

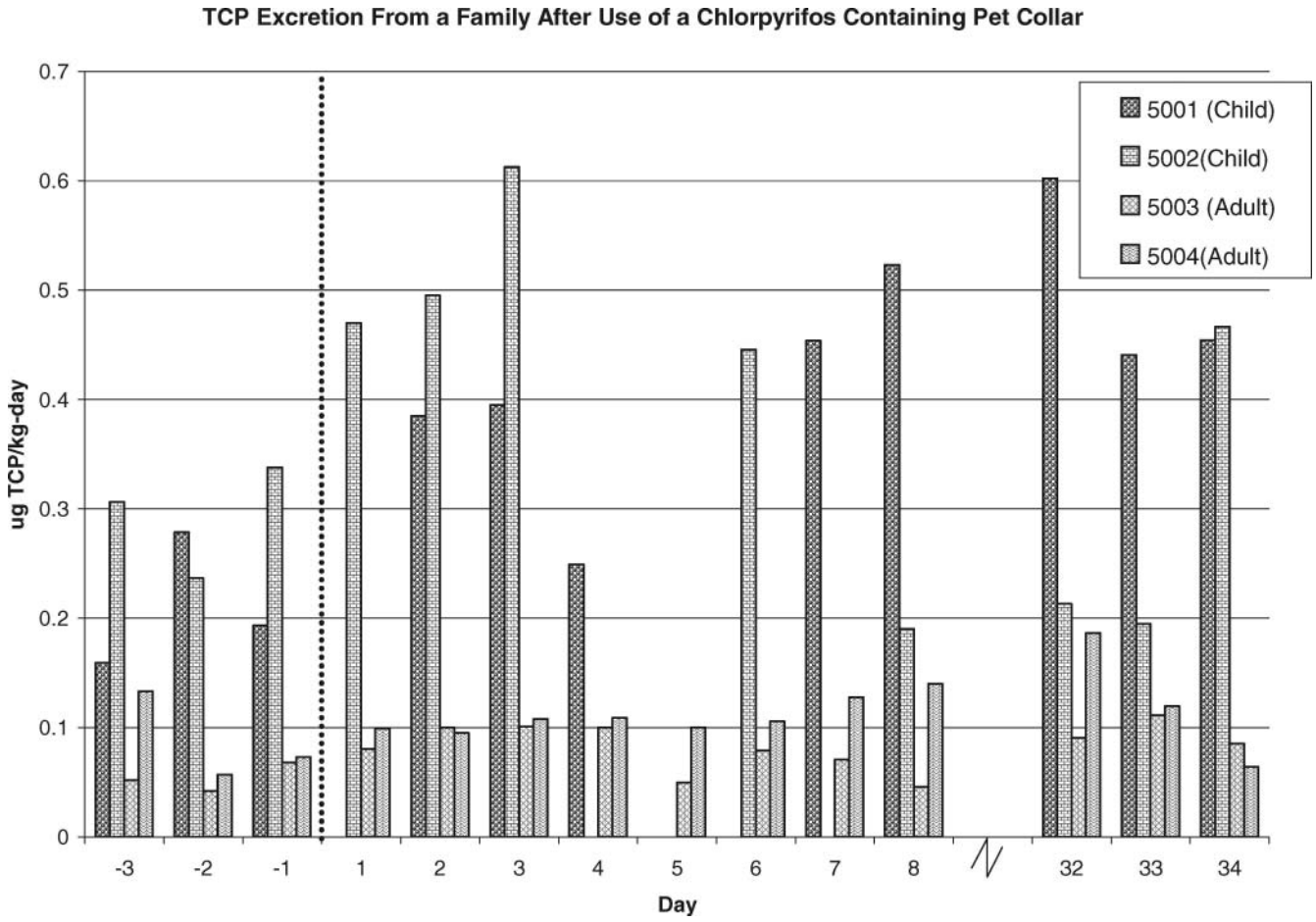

Fig. 4. TCPy excretion in a family after use of pet collars containing chlorpyrifos in μg TCPy/kg/d. Interestingly, children 5001 and 5002 had no known direct contact with the dogs wearing the flea collars.

family household. Morgan et al.[15] first investigated the potential human exposure from pet-borne insecticides carried indoors. Diazinon residues were transferred from outdoor turf treatments to inside the home, as well as to adult and child occupants. Our current findings further support the possible role that pets may have as a point source for residential pesticide exposure of children and adults.[16]

Estimates of Exposure

It is instructive to relate the exposures reported here to chlorpyrifos equivalents and risk assessment end points. In all cases TCPy was found in pre-application urine specimens of adults and children in small amounts (0.02 to 0.27 μg TCPy/kg-d) that would represent about 0.8 to 57 ug TCPy/g creatinine (assuming a 70 kg male excretes 1.7 g creatinine/d).[10] The higher hypothetical level is about 33 times greater than the geometric mean of the TCPy/g creatinine of the general population cited in the 2005 CDC Third National Report on Human Exposure to Environmental Chemicals.[17] Post application monitoring following use of chlorpyrifos collars and shampoos usually resulted in increased levels of biomarker excretion (0.19 – 0.68 μg TCPy/kg-d). TCPy urinary excretion rates (μg TCPy/kg-d) in the 3- and 5-year old children were higher following use of collars or shampoos than pre-use levels, but the differences can only be viewed as trends.

The 1997 USEPA Standard Operating Procedure offered additional procedures for setting bounding limits on human exposure related to pet product use. When data were lacking ten per cent of active ingredient applied to the pet by the homeowner during dipping, dusting and shampooing was the assumed potential external dose of applicators as a default assumption.[18] In addition, dermal and inhalation exposure due to handling of flea collars was estimated to be one percent of the active ingredient applied.[18] Table 1 provides the estimated daily dose and corresponding TCPy excretion of human chlorpyrifos exposure from liquid pet treatment (shampoo) and dog collar use. These bounding estimates are substantially greater than the corresponding

Table 1. USEPA Standard Operating Procedure Estimates of Human Chlorpyrifos Exposure from Liquid Pet Treatment and Dog Collar Use.

	Source strength 1	*Amount per use 2*	*Active ingredient available 3*	*Dosage chlorpyrifos (mg/kg-d) 4*	*Equivalent TCPy (mg/kg-d) 5*
			Shampoo		
Adult 70 kg	3.84% chlorpyrifos	60 mL/3.8 L	10%	3.29	1.86
Child 35 kg				6.58	3.73
			Collar		
Adult 70 kg	8.0% chlorpyrifos	43 g	1%	0.49	0.28
Child 35 kg				0.98	0.56

Chlorpyrifos Dosage (mg/kg-d) = (1 *x* 2 *x* 3) *x* (1000 mg/g) /body weight = 4.
Equivalent TCPy (mg/kg-d) = 4 *x* MW TCPy/MW CP = 4 *x* 198.5/350.6 = 5.

TCPy excretion levels recorded in these pilot biomonitoring studies.

Discussion

Although chlorpyrifos is no longer used in pet care products in the United States, there continues to be consumer demand for sprays, powders, dusts, shampoos, collars, and spot-on treatments for dogs and cats that contain a variety of active ingredients.[6] Some active ingredients include pyrethrins, synthetic pyrethroids (phenothrin, etofenprox; Hartz®), organophosphorous insecticides (tetrachlorvinfos; Hartz®), neonicotinoids, (imidacloprid; Advantage®), avermectins (selemectin; Revolution®) and a phenylpyrazole insecticide (fipronil; Frontline®). The low human exposure potential of chlorpyrifos shampoos and dips and flea collars that were the subject of these pilot studies represent a useful estimate of the analytical sensitivity needed for future exposure assessment research for similar products.

In general, persons who had contact with pets treated with chlorpyrifos flea protection products had small increases in the excretion of TCPy, the well-characterized exposure urinary biomarker.[11,19,14] Following use of shampoos or flea collars, urinary TCPy levels in applicators or family members were well below biomarker levels expected to be associated with adverse effects or depressed levels of cholinesterases, an alternate indicator of chlorpyrifos exposure in pet product studies.[20] Our pilot studies were opportunistic and involved small numbers of participants who used products according to label directions. The results demonstrated very limited human exposure following use of this class of flea control products.

The results of Studies 1 and 2 showed the importance of activity pattern on insecticide exposure. The applicator excretion of TCPy in Study 1 was higher during the 6-day monitoring period as was the urine TCPy level of the 11 year-old child who had substantial play activity with the pet. The head of household was absent during the day and had little contact with the treated dog and registered only background levels of biomarker. Similar results were obtained in Study 2. Again the children recorded higher levels of biomarker than their parents. The head of household who was absent during the day did not register elevated biomarker levels. On this basis the pattern of response gives indirect support to the importance of indoor activity as a determinant of exposure.

Chambers and colleagues[20] have studied greater rates of application on dogs under experimental conditions with respect to the transferability of insecticide as a measure of potential for human exposure. Boone et al.[1] determined the amount of chlorpyrifos that could be transferred to cotton gloves following treatment of dogs in a commercial dipping facility. Residues accumulated on gloves dissipated from 971 μg chlorpyrifos at 4h to 26 μg after three weeks. Boone et al.[21] later conducted similar dog dipping studies with phosmet. Experimental differences in transferable residue levels were attributed to fur saturation of the dogs during dipping and rubbing pressure among the samplers. Serum cholinesterase was inhibited by chlorpyrifos dipping, but it was unchanged by the phosmet treatments either due to lack of absorption, detoxification or the inherent sensitivity of serum cholinesterase. In either case, the commercial dipping using these organophosphorous insecticides was not associated with substantial exposure (indicated by anticholinesterase activity). The amounts of organophosphorous insecticides applied during commercial dipping[1,21,22] were likely much greater than applications made by participants in our present pilot studies in which the dogs were treated by pet owners at their private residences using over-the-counter products.

In Studies 3 and 4 urine biomonitoring followed application of chlorpyrifos-impregnated flea collars to dogs primarily living freely indoors during the day. In the first case no increase in urinary TCPy excretion was observed in the parent who applied the collar and was absent during the day. Higher TCPy excretion was observed in the child after collar use. A series of urine specimens collected from

Table 2. Chlorpyrifos Biomonitoring Following Pet Product Use and Results of Third National Report on Human Exposure to Environmental Chemicals[17].

				Results of this study			
	CDC TCPy US population 2001–2002			*Collars (μg/kg-d)*		*Shampoo (μg/kg-d)*	
	μg/g creatinine	*μg/d*	*μg/kg-d*	*Pre*	*Post*	*Pre*	*Post*
3 year-old	–	–	–	0.24–0.34	0.19–0.61	–	–
5 year-old	–	–	–	0.15–0.27	0.25–0.60	–	–
11 year-old	3.48[a]	3.06	0.28	0.25–0.27	0.30–0.68	0.01–1.36	0.28–3.92
Adult Males	1.71	2.91	0.04	0.02–0.13	0.02–0.11	0.03–0.05	0.02–0.07
Adult Females	1.75	1.75	0.03	0.05–0.13	0.06–0.19	0.05–0.07	0.08–0.17

[a]Data from children aged 6–11 years using the Geometric Mean reported in 2005 from data collected in 2001–2002.

the dog clearly demonstrated chlorpyrifos absorption (sufficient that the analyst remarked about abnormally high TCPy levels in this particular batch of coded samples!).

Study 4 was also characterized by low level TCPy excretion by adults and children alike. Since there was no direct contact between the children and the collared dogs, we suggest that the indoor environment where both played became contaminated with the insecticide. Subsequent contact-transfer resulted in the minimal increased TCPy excretion that was observed.

In the Chambers' research using pet collars, the study period was determined by the suggested product lifetime.[20] Transferability of chlorpyrifos was measured by rubbing the fur on the neck and back of the dogs at the application site. Chlorpyrifos was maximally transferable to cotton gloves and tee shirts worn by volunteers within 2 weeks of flea collar application.[5] Post-application levels were significantly greater than preapplication levels of chlorpyrifos, but there was no evidence of absorption based upon TCPy urinary excretion. Urine specimens were collected before collar application and on days 3, 7, 28, 84, and 168 after the collar was applied. Maximal transfer of chlorpyrifos from the collar area to gloves occurred on days 16 to 21 based upon petting studies. Biomonitoring in our pilot studies included all family members and represented a preapplication and a much shorter post-application period. The small increases in urinary TCPy (Fig. 4) associated with flea collar use may result from direct contact with the collar as well as chlorpyrifos distribution on the peltage of the dogs and its transfer to the environment or the pet owner. We concur with Chambers et al.[5] that there is very little evidence that use of the chlorpyrifos flea collar resulted in enhanced exposure of adults or children.

Earlier studies using cotton gloves as passive dosimeters demonstrated transferable residues on dogs from 0 to 5599 total μg of active ingredient that decline with time following treatment of dogs with flea dip (Fig. 1). Transferable chlorpyrifos residues and TCPy excretion were measured on dogs with flea collars.[5] Our range of TCPy excretion when normalized to creatinine (1.0–40.9 ng/mg creatinine) is similar to those reported by Chambers et al.[5] Comparison of the pilot biomonitoring data with the CDC monitoring (Table 2) and the calculated default post application exposure estimates (Table 1) each register pest product use as an activity with relatively low human exposure potential.

Here we report pilot studies of peoples' excretion of TCPy following their use of pet collars and shampoos or dips containing chlorpyrifos. Although chlorpyrifos products are no longer available in the United States, these results represent the low human exposure potential of these and similar products for the treatment and control of pests of companion animals. It is important to note that direct correlation between transferable residue and absorbed dose is problematic as gloves do not represent dermal absorption, but are a means of demonstrating residue availability. Biomonitoring is essential to correlate availability with dermal absorption. These observations of TCPy excretion following use of pet collars and shampoos or dips containing chlorpyrifos do not assess the elusive link between residue availability on pets and glove transferability.

Pet collars and shampoos or dips containing chlorpyrifos when used as directed apparently lead to very low-level exposures of adults and children who have direct or indirect (environmental) contact with the treated companion animals. TCPy excretion in children in this study was up to four-fold higher than biomarker levels excreted by adults in the same household. However, the higher exposures in children do not appear to be directly related to more animal contact, but from higher activity levels in the home where companion animals can introduce pesticides into the home. The chlorpyrifos biomarker levels following use of pet products were similar to those observed in other indoor pesticide studies.[9] The occurrence of TCPy as a marker of dietary exposure reduces the specificity of these analyses since the diet is a continuing source of biomarkers.[14] In spite of this limitation, the temporal relationship between

urine TCPy levels and flea product use in these pilot studies signals that similar pet products can contribute to the aggregate pesticide exposure of adults and children.

Acknowledgments

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