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Captan Exposure and Evaluation of a Pesticide Exposure Algorithm among Orchard Pesticide Applicators in the Agricultural Health Study

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Pesticide exposure assessment in the Agricultural Health Study (AHS) has relied upon two exposure metrics: lifetime exposure days and intensity-weighted lifetime exposure days, the latter incorporating an intensity score computed from a questionnaire-based algorithm. We evaluated this algorithm using actual fungicide exposure measurements from AHS private orchard applicators. Captan was selected as a marker of fungicide exposure. Seventy-four applicators from North Carolina and Iowa growing apples and/or peaches were sampled on 2 days they applied captan in 2002 and 2003. Personal air, hand rinse, 10 dermal patches, a pre-application first-morning urine and a subsequent 24-h urine sample were collected from each applicator per day. Environmental samples were analyzed for captan, and urine samples were analyzed for *cis*-1,2,3,6-tetrahydrophthalimide (THPI). Task and personal protective equipment information needed to compute an individual's algorithm score was also collected. Differences in analyte detection frequency were tested in a repeated logistic regression model. Mixed-effects models using maximum-likelihood estimation were employed to estimate geometric mean exposures and to evaluate the measured exposure data against the algorithm. In general, captan and THPI were detected significantly more frequently in environmental and urine samples collected from applicators who used air blast sprayers as compared to those who hand sprayed. The AHS pesticide exposure intensity algorithm, while significantly or marginally predictive of thigh and forearm captan exposure, respectively, did not predict air, hand rinse or urinary THPI exposures. The algorithm's lack of fit with some exposure measures among orchard fungicide applicators may be due in part to the assignment of equal exposure weights to air blast and hand spray application methods in the current algorithm. Some modification of the algorithm is suggested by these results.

Keywords: agriculture; benomyl; captan; exposure assessment; fungicide; occupational; orchard; pesticide; thiophanate-methyl

INTRODUCTION

Exploratory results from the Agricultural Health Study (AHS) indicated that fungicide use was associated with increased risk of self-reported retinal degeneration among farmers who applied pesticides and the wives of farmer applicators (Kamel *et al.*, 2000; Kirrane *et al.,* 2005). For AHS applicators and wives who grew orchard fruit, increased risk of self-reported retinal degeneration was found only in those who used fungicides. These initial findings led to an interest in understanding fungicide exposures among orchard pesticide applicators in the AHS.

Captan, a fungicide frequently used in orchards, was selected as a marker of fungicide exposure. Captan is typically applied in orchards by either air blast or hand spray. Captan was first registered for use in the US in 1951 (USEPA, 1999). By 2003, captan had become the second most abundantly applied fungicide on apples and peaches in the US (USDA, 2004). The US Environmental Protection Agency

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(EPA) has classified captan as a category I toxicant for being severely irritating to the eyes (USEPA, 1999). Captan has a short half-life in human blood (0.97 s) (Gordon *et al.*, 2001), suggesting that it may not reach target organs at sufficient levels to be carcinogenic. EPA has classified captan as not likely to be a human carcinogen except following prolonged high-level exposures (Federal Register, 2004).

Captan's metabolism has been described in humans (Krieger and Thongsinthusak, 1993). After oral administration, the captan metabolites *cis*-1,2,3,6-tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA) are excreted into the urine (Fig. 1). THPI is eliminated mostly within 24-h at both high (1 mg kg^{-1}) and low (0.1 mg kg^{-1}) doses. While the fraction of the dose in urine is higher for TTCA (4–9%) than for THPI (1–2%), THPI is stable at a detection limit (LOD) an order of magnitude lower than TTCA. The dermal absorption rate of captan in rats is ~9.6% per 24 h (0.4% per hour) (USEPA, 1999; Gordon, 2001). Urinary THPI has been used as a biomarker of captan exposure among agricultural workers (Winterlin *et al.*, 1984, 1986; van Welie *et al.*, 1991; de Cock *et al.*, 1995; Krieger and Dinoff, 2000).

The National Institute for Occupational Safety and Health (NIOSH) conducted an exposure study in 2002 and 2003 among 74 AHS private pesticide applicators growing apples or peaches. The AHS is a cohort of 57 311 licensed pesticide applicators in Iowa and North Carolina and 32 347 spouses of the private applicators (Alavanja *et al.*, 1996). The NIOSH study included environmental monitoring for captan and biological monitoring for THPI, with repeated measurements on applicators because of previously reported high within-worker variability among Dutch orchard applicators (de Cock *et al.*, 1998). Exposure to two less frequently used orchard fungicides, thiophanate-methyl (TPM) and benomyl, which can be used with captan, was also monitored. Benomyl was voluntarily withdrawn from the market in 2001; however, we anticipated that applicators would use existing supplies during the study period. Our study also provided an opportunity to use actual exposure measurements to evaluate an AHS algorithm intended to give quantitative estimates of pesticide exposure intensity (Dosemeci *et al.*, 2002). In this paper, we report monitoring results for the three fungicides and our evaluation of the AHS general pesticide exposure intensity algorithm. The application and mixing practices of the applicators have been previously described (Hines *et al.*, 2007).

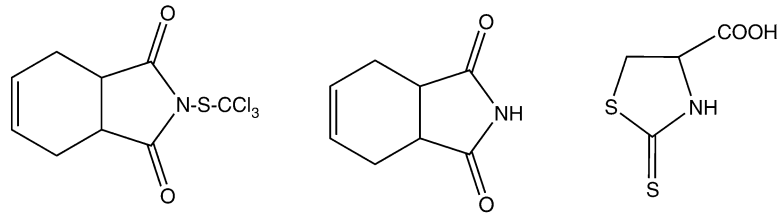
MATERIALS AND METHODS

Study population

Seventy-four AHS private applicators (1 female, 73 males) who grew either apples and/or peaches in Iowa ($n = 21$) or North Carolina ($n = 53$) participated in the study. Selection and recruitment procedures have been previously described (Hines *et al.*, 2007). All participants, except one, sprayed captan during the study period by either air blast or hand spray. Participation was voluntary and informed consent was obtained. This study was approved by all appropriate Institutional Review Boards.

Sample collection

Applicator sampling was conducted on 2 days at least 7 days apart. A personal air, hand rinse, 10 dermal patches, a pre-application first-morning urine and a subsequent 24-h urine sample were collected from each applicator on each sampled day. Breathing-zone air samples were collected on XAD-2 OSHA Versatile Samplers (OVS) (with quartz prefilters) (SKC, Inc., Eighty Four, PA, USA) at a nominal flow rate of 1 Lpm. Sampling pumps were pre- and post-calibrated using a Dry Flow® DC-Lite primary flow calibrator (Bios Int., Butler, NJ, USA). Patch samplers were attached to clothing or skin at 10 locations (right thigh, left thigh, right



Captan	THPI	TTCA
N-trichloromethylthio-4-cyclohexene-1,2-dicarboximide	Tetrahydrophthalimide	Thiazolidine-2-thione-4-carboxylic acid
$C_9H_8Cl_3NO_2S$ MW=300.6	$C_8H_9NO_2$ MW=151.17	$C_4H_5NO_2S_2$ MW = 163.2

Fig. 1. Chemical structures of captan and two of its human metabolites.

lower leg, left lower leg, right forearm, left forearm, right shoulder, left shoulder, chest and back) and removed after pesticide handling activities. A patch sampler consisted of a 10 × 10 cm piece of Texwipe® AlphaWipe® polyester clean room wipe (Fisher Scientific, Pittsburgh, PA, USA) inserted into a lightweight chipboard holder with a 7.6-cm diameter circle cut in one side (45.4 cm^2 sampling area). The patch was transferred to a 50-ml polypropylene centrifuge tube (Fisher Scientific) using clean forceps. Air and patch samples were collected for the duration of pesticide handling activities. A hand rinse was performed at the end of pesticide handling activities on the dominant hand (except for hand spray where the hand holding the wand was sampled). The hand was inserted into a polyethylene bag (30.5 × 20.3 × 0.01 cm thickness, Fisher Scientific) containing 150 ml of 100% isopropanol (IPA). The bag was secured around the wrist and the hand was shaken at a constant rate for 30 s. The sample was poured into a 250-ml jar with a polytetrafluoroethylene-lined (PTFE) cap. Only one hand was rinsed to minimize interference with the biological monitoring.

On each sampling day, applicators collected all urine starting with that day's first-morning void (Day 0) through the first-morning void of the next day (Day 1). Urine was collected in five time periods: wake-up Day 0, wake-up to 12 p.m. Day 0, 12 p.m. to 6 p.m. Day 0, 6 p.m. to 12 a.m. Day 0 and 12 a.m. to wake-up Day 1. Applicators were provided with a cooler containing five, 500 ml high-density polyethylene bottles labeled by time period, refrigerant gel packs, pen and instructions. Applicators were instructed to record all void times. Urine volume was measured with a clean 250-ml graduated cylinder.

Air, hand rinse and patch samples were stored cold (4°C) prior to analysis. Urine aliquots were frozen and shipped on dry ice, then stored at −80°C. Applicators were reimbursed $50 for each sampled day for their time and inconvenience.

Sample analysis

Captan was determined in air, hand rinse and dermal patch samples by high-performance liquid chromatography (HPLC) with confirmation by gas chromatography/mass spectrometry (GC/MS) according to NIOSH methods 5606, 9202, 9205 and 9208 (NIOSH, 2003). Briefly, front and back air sample sections were extracted with 2 ml of 60% acetonitrile:40% IPA (v/v), and patch samples were extracted with 30 ml of 0.2% triethylamine-PO_4 preservative (pH 7.0 ± 0.1):40% IPA:59.8% acetonitrile (v/v/v). Air and patch extracts were tumbled end-over-end for 1 h and filtered. No extraction was needed for the hand rinses; however, a 1-ml aliquot of each hand rinse was filtered.

Captan was initially quantified in air, hand rinse and dermal patch samples by reverse-phase HPLC-UV at a wavelength of 200 nm. The insecticide phosmet interfered with captan determination by HPLC. Therefore, all samples with a positive response at the retention time of captan were submitted for confirmatory quantitation by GC/MS. Remaining samples were considered non-detectable for captan. THPI, a captan hydrolysis product, was detected by GC/MS in the samples. The amount of hydrolyzed captan was estimated by multiplying the amount of THPI by the molecular weight ratio of captan to THPI (300.59/151.17 = 1.99). Intact captan was equivalent to the amount of unhydrolyzed captan detected as captan. Estimated total amount of captan in the sample was the sum of intact and hydrolyzed captan. Captan LODs by GC/MS are given in Table 1. TPM and carbendazim, a benomyl hydrolysis product, were analyzed in air, hand rinse and patch samples by the above HPLC method. After reviewing quality control (QC) results, only hand rinse data are reported for TPM and carbendazim. LODs for TPM and carbendazim in hand rinse samples were 40–500 and 40–380 μg per sample, respectively.

THPI was isolated from urine by solvent extraction (Morse Laboratories, 2001). An aliquot of the urine was acidified with phosphoric acid and diluted with 0.01% Aerosol® OT-75 solution. Solid sodium chloride was then added, and the mixture extracted three times with dichloromethane (DCM). The DCM extracts were combined, concentrated and then purified by means of nuchar:silica liquid chromatographic column cleanup. The eluate was evaporated to dryness, reconstituted in toluene and submitted for gas chromatography. Detection and quantitation were conducted using a gas chromatograph equipped with a mass selective detector. The THPI LOD was 1.7 μg l^{-1}. Creatinine was measured in urine using a modified Jaffé kinetic rate method (Heinegård and Tiderström, 1973).

Blind QC samples included laboratory-fortified samples, field-fortified samples and urine sample splits (one per applicator day). Two sets of air and patch field-fortified samples were prepared; one set was exposed to ambient field conditions in a non-spray area, the other left unexposed at staff offices. Field blanks (10%) were prepared in a manner similar to field samples.

Data analysis

Analyses were done in SAS v. 9.1.3 (SAS Institute, Inc., Cary, NC, USA). Statistical significance was set at 0.05. The percentage of samples with captan or THPI below their respective LODs was determined. Where this percentage exceeded 50, only the 95th percentile and range of values greater than the LOD were reported. Data were skewed to the right and a natural

Table 1. Captan levels in air, hand rinse and patch samples by application method

	Air blast						Hand spray					
	n	% ≥LOD[a]	GM[b] (95% CI)	GSD	95th percentile	Range of values >LOD	*n*	% ≥LOD	GM (95% CI)	GSD	95th percentile	Range of values >LOD
Air (μg m^{-3})	78	61.5***	29 (17–47)	5.1	440	7.9–1500	61	32.8	NE	NE	47	12–120
Hand (μg)	78	70.5**	540 (309–950)	6.8	7900	75–12000	63	34.9	NE	NE	1300	120–12000
Patch (μg)												
R thigh	79	54.4	35 (14–89)	15	3000	15–9300	60	36.7	NE	NE	1700	26–2500
L thigh	78	47.4	NE	NE	2300	24–4300	59	37.3	NE	NE	2800	20–4500
R lower leg	74	35.1	NE	NE	1500	15–7000	59	30.5	NE	NE	1500	64–2200
L lower leg	75	30.7	NE	NE	740	13–2000	59	30.5	NE	NE	1600	15–2500
R forearm	79	58.2	45 (23–88)	9.0	1800	20–6000	61	39.3	NE	NE	1000	15–4000
L forearm	79	57*	46 (24–87)	7.8	1300	15–3500	62	27.4	NE	NE	600	20–5400
R shoulder	79	38	NE	NE	740	18–1700	61	23	NE	NE	360	40–2200
L shoulder	78	38.5	NE	NE	750	17–2700	61	23	NE	NE	360	36–5400
Chest	79	40.5	NE	NE	640	13–2400	60	21.7	NE	NE	550	40–3400
Back	78	29.5	NE	NE	270	14–860	62	17.7	NE	NE	160	40–2600

n = number of days; NE = not estimated, >50% of the observations below the LOD; R = right; L= left.

[a]LOD's = air: 0.4–2 μg per sample; hand: 30–200 μg per sample; patches: 6–30 μg per sample.

[b]GM, GSD and 95% CI were estimated using MLE via PROC NLMIXED with person treated as a random effect. The data were left censored at the LOD. The log-normal distribution was specified in the model.

*$P < 0.05$ air blast compared to hand spray; **$P < 0.01$ air blast compared to hand spray; ***$P < 0.001$ air blast compared to hand spray.

log transformation was applied. Maximum-likelihood estimation (MLE) was used to treat data below the LOD, except where noted. The geometric mean (GM), geometric standard deviation (GSD) and 95% confidence interval (CI) were estimated for each exposure measure using a mixed model via PROC NLMIXED to account for left-censoring and repeated measures (Thiébaut *et al.*, 2006). A compound symmetric covariance structure was used in all models.

We computed the THPI unadjusted concentration ($\mu g\ l^{-1}$), creatinine-adjusted concentration ($\mu g\ g^{-1}$), mass (μg) and excretion rate ($\mu g\ h^{-1}$) for each urine collection time period. For the 24-h period, we computed the THPI unadjusted concentration ($\mu g\ l^{-1}$), total mass (μg) and total mass adjusted for body weight ($\mu g\ kg^{-1}$ body weight). The total mass of THPI excreted in 24 h (μg) was determined by summing the mass of THPI in all urine samples collected after the first-morning void on Day 0 through the first-morning void on Day 1. The concentration of THPI in the 24-h sample ($\mu g\ l^{-1}$) was computed by dividing the 24-h THPI mass by the total 24-h urine volume. THPI excretion rate ($\mu g\ h^{-1}$) was computed by dividing the mass of THPI in the sample by the elapsed time between the last void for the sample and the prior sample. The number of cases where all four samples were below the LOD was evaluated as an indicator of censoring in the 24-h summed variable. MLE for treating left-censored data was not feasible for the 24-h urine measures because the 24-h value was the sum of several samples; rather, censored values were replaced with LOD/2, the samples summed and the GM, GSD and 95% CI estimated via PROC MIXED with person treated as a random effect. Differences in the proportion of samples below the LOD were tested using a repeated logistic regression model with person treated as a random effect. Correlation among log-transformed exposure measures was tested using Pearson's correlation coefficient.

The AHS general pesticide exposure intensity algorithm has four components: mixing status [MIX], application method [APPLY], equipment repair status [REPAIR] and personal protective equipment [PPE] (Dosemeci *et al.*, 2002). [MIX], [APPLY] and [REPAIR] are summed, then multiplied by a [PPE] reduction factor [equation (1)].

$$\text{Exposure intensity score} = (\text{MIX} + \text{APPLY} + \text{REPAIR}) \times \text{PPE}. \quad (1)$$

[MIX], [APPLY] and [REPAIR] are assigned exposure weights reflecting the extent to which the component contributes to exposure, with higher weights indicating greater exposure. PPE use was grouped into eight categories reflecting the amount and type of PPE worn. Each category was assigned an exposure reduction factor. Algorithm exposure weights and reduction factors are given in Appendix 1.

To evaluate the algorithm against measured exposure data, field observers collected information on application method used, whether the applicator mixed and types of PPE worn. Applicators were also asked if they had repaired spraying equipment during the monitored period. PPE use was recorded separately for mixing and applying. In computing the algorithm exposure intensity score, the smaller (more protective) [PPE] reduction factor for mixing and applying was used (PPE was not asked separately for mixing and applying in the AHS enrollment questionnaire; therefore, questionnaire-based algorithm scores reflect PPE use at any time during pesticide handling). On one day, a single applicator mixed the day before application, and an intermediate weight of 6 was assigned to [MIX]. Air, hand rinse, the four patch locations with the highest detection frequency, THPI mass and concentration in the 24-h sample, THPI mass in the first-morning Day 1 sample and THPI excretion rate overnight (Day 0 to Day 1) were evaluated against the algorithm in a mixed model via PROC NLMIXED with the algorithm score as the independent variable and the log-transformed exposure measure as the dependent variable. We also used mixed models to examine the influence of [MIX], [REPAIR] and [PPE] as independent variables on the above dependent variables. [APPLY] was not included because it did not vary across applicators.

RESULTS

Air, hand rinse and patch

Captan results for air, hand rinse and patch samples by application method are shown in Table 1. Captan was detected significantly more frequently in air and hand rinse samples from applicators who airblasted as compared to those who hand sprayed (air: 61.5 versus 32.8%; hand rinse: 70.5 versus 34.9%). Among air blast users, the GM air and hand rinse captan exposures were 29 $\mu g\ m^{-3}$ and 540 μg, respectively. GM captan levels were not estimated for hand spray as detection frequencies were $<50\%$. The GM captan air level (29 $\mu g\ m^{-3}$) was $<1\%$ of the NIOSH and American Conference of Governmental Industrial Hygienists recommended exposure limit of 5 $mg\ m^{-3}$, while the maximum air level (1500 $\mu g\ m^{-3}$) was 30% of the limit (NIOSH, 1992; ACGIH, 2006).

Captan was also detected more frequently for air blast (range 29.5–58.2%) than for hand spray (range 17.7–39.3%) at most dermal patch locations; however, only the left forearm was significantly different

(Table 1). Patch detection frequency for the two application methods was most similar for the lower legs. Among air blast applicators, the GM captan exposures to the three patch locations with a detection frequency of at least 50% were 35 μg (right thigh); 45 μg (right forearm) and 46 μg (left forearm). Patch captan levels at the 95th percentile were higher for air blast than for hand spray, except for the left thigh and the lower leg patches. On days where applicators completed spraying with a full set of patches (n = 124), captan was detected on all 10 patches on 28% of the days and on none of the patches on 15% of the days. GSD estimates indicated that captan levels among air blast users were more variable on patches than in air or hand rinses.

TPM was detected in hand rinses on 8 (29.6%) of the 27 days it was sprayed. Detectable TPM levels ranged from 100 to 460 μg per sample. Carbendazim was detected in hand rinses on 5 (29.4%) of the 17 days benomyl was sprayed. Detectable carbendazim levels ranged from 68 to 620 μg per sample.

Urine

Total 24-h creatinine was used to check for completeness of urine collection. Mean (±SD) 24-h creatinine was 1.59 ± 0.54 g l^{-1} (n = 131, range 0.51–3.76 g). For adult males, 24-h creatinine is reported to range from 0.5 to 3.0 g per 24 h (Alessio *et al.*, 1985; Boeniger *et al.*, 1993). A 24-h sample with a total creatinine of only 0.27 g was excluded from all 24-h urine analyses due to probable incomplete urine collection. Applicator mean (±SD) weight was 88 ± 16 kg (range 60–148 kg).

THPI results are presented by application method (Table 2). For both air blast and hand spray, THPI detection frequency was lowest in the wake-up Day 0 sample (31.9 and 13.8%, respectively) and highest in the wake-up Day 1 sample (77.2 and 40.7%, respectively). THPI was detected significantly more frequently in all urine collection time periods for applicators using air blast as compared to hand spray. Across collection time periods, maximum THPI values were 32 μg l^{-1} (unadjusted concentration, air blast, wake-up Day 1), 60.5 μg g^{-1} (creatinine-adjusted concentration, hand spray, wake-up Day 1), 13.3 μg (mass excreted, air blast, evening Day 0) and 4.19 μg h^{-1} (excretion rate, air blast, evening Day 0). For air blast, mean THPI concentration and mass increased during the day with the highest levels found in the wake-up sample on Day 1; however, the mean excretion rate peaked on the evening of Day 0. Unadjusted THPI concentrations averaged <5 μg l^{-1} across all collection time periods.

For air blast users, the GM THPI concentration in the 24-h sample was 3.55 μg l^{-1}. The percentage of days where all samples comprising the summed 24-h total had levels below the LOD was 24% for air blast and 55% for hand spray. Mean THPI levels were not estimated for hand spray as detection frequencies were <50%. Air, hand rinse, thigh patch and forearm patch samples were all significantly correlated with 24-h urine measurements (Table 3). The hand rinse sample had the highest correlation of any external exposure measure with 24-h THPI concentration and mass (Pearson r = 0.62 and 0.57, respectively).

Quality control

Mean captan and THPI recovery [relative standard deviation (RSD)] ranged from 88 to 104 (5.4–15)% and 80–86 (9.1–13)%, respectively (Appendix 2). The urine splits had a THPI RSD of 8.1%. Captan recovery differences between ambient-exposed and unexposed samples were small, indicating little, if any, captan loss due to environmental conditions. Mean TPM recoveries in exposed air and patch samples were significantly lower than unexposed samples (t-test, air: P = 0.001; patch: P = 0.0005, data not shown). Mean carbendazim recoveries in exposed and unexposed air and patch samples were excessively high (i.e. >125%, data not shown). Therefore, only hand rinse results are reported for TPM and carbendazim. Results have not been adjusted for field recovery.

Algorithm evaluation

Algorithm exposure intensity scores ranged from 1.8 to 20, with 28% of the scores <5, 38% from 5 to 10 and 34% >10. Application [APPLY] was by air blast (55%), hand spray (44%) and mist blower/fogger (1%) (Hines *et al.*, 2007). Mean algorithm scores for applicators who used air blast versus hand spray were 8.2 and 8.8, respectively. These means were not significantly different (t-test, P = 0.55). Applicators personally mixed on 97% of the days (Hines *et al.*, 2007). Thus, little variability was present in [MIX]. Repair of spraying or mixing equipment [REPAIR] was reported on 18% of the days (Hines *et al.*, 2007). PPE use was more variable. The percentage of applicators using the various combinations of the three [PPE] categories is given in Table 4. The two [PPE] reduction factors with the highest percentage of days, 0.1 (25.7%) and 1.0 (25%), were at the extremes of the scale.

The algorithm was a significant predictor of increased right and left thigh patch exposures (P = 0.0003 and P = 0.0084, respectively) and marginally predictive of increased right and left forearm exposures (P = 0.08 and P = 0.10, respectively) (Table 5). The algorithm, however, did not predict air, hand rinse and urine exposures. We also evaluated the algorithm against all urine measures for those who

Table 2. THPI levels in urine by application method

	Air blast						Hand Spray					
	n	% ≥LOD[a]	GM[b] (95% CI)	GSD	95th percentile	Range of values >LOD	*n*	% ≥LOD	GM (95% CI)	GSD	95th percentile	Range of values >LOD
By collection period												
Conc., μg l^{-1}												
Wake-up, Day 0	72	31.9*	NE	NE	11.7	1.8–17.0	58	13.8	NE	NE	4.4	2.0–13.2
Morning	69	43.5*	NE	NE	8.4	1.74–15.1	56	21.4	NE	NE	7.4	1.77–10.7
Afternoon	74	67.6***	2.96 (2.18–4.01)	2.7	14.2	1.86–17.3	62	30.6	NE	NE	10.3	2.22–17.0
Evening	75	76***	4.05 (2.93–5.59)	2.9	24.4	1.73–28.0	63	38.1	NE	NE	11.1	1.67–29.9
Wake-up Day 1[c]	79	77.2**	4.17 (2.98–5.85)	3.1	21.7	1.74–32.0	59	40.7	NE	NE	15.6	1.77–22.9
Conc., adjusted for creatinine, μg g^{-1}												
Wake-up, Day 0	72	31.9*	NE	NE	6.6	0.89–9.7	58	13.8	NE	NE	6.8	0.86–18.7
Morning	69	43.5*	NE	NE	8.8	1.51–29.2	56	21.4	NE	NE	7.7	0.77–22.8
Afternoon	74	67.6***	1.60 (1.12–2.28)	3.2	9.6	0.63–19.2	62	30.6	NE	NE	6.0	0.71–8.8
Evening	75	76***	2.37 (1.68–3.35)	3.2	13.6	1.04–18.7	63	38.1	NE	NE	6.8	0.77–35.6
Wake-up Day 1	79	77.2**	2.90 (2.05–4.09)	3.2	17.1	0.54–35.2	59	40.7	NE	NE	11.3	1.17–60.5
Mass, μg												
Wake-up, Day 0	71	32.4*	NE	NE	2.3	0.30–6.8	58	13.8	NE	NE	1.1	0.26–5.8
Morning	69	43.5*	NE	NE	3.0	0.11–6.5	54	20.4	NE	NE	1.2	0.17–3.7
Afternoon	74	67.6***	0.55 (0.36–0.85)	4.0	5.3	0.19–7.2	62	30.6	NE	NE	2.1	0.15–5.3
Evening	75	76***	0.89 (0.62–1.27)	3.4	5.1	0.25–13.3	63	38.1	NE	NE	2.7	0.20–9.8
Wake-up Day 1	79	77.2*	1.29 (0.91–1.84)	3.3	6.3	0.23–10.2	59	40.7	NE	NE	4.7	0.41–8.7
Excretion rate, μg h^{-1}												
Morning	57	43.9*	NE	NE	0.86	0.02–1.06	45	22.2	NE	NE	0.31	0.08–0.78
Afternoon	58	70.7**	0.10 (0.067–0.16)	3.9	0.84	0.04–1.15	45	33.3	NE	NE	0.30	0.03–0.89
Evening	62	77.4**	0.17 (0.12–0.24)	3.4	0.87	0.06–4.19	52	42.3	NE	NE	0.65	0.03–2.34
Overnight	64	76.6*	0.16 (0.11–0.24)	3.4	0.87	0.04–1.19	51	39.2	NE	NE	0.64	0.05–0.97
24-h composite												
Conc., μg l^{-1}	72	NA[d]	3.55 (2.65–4.76)	2.7	17.8	0.85–21.3	56	NA	NE	NE	10.5	0.85–13.5
Mass, μg	72	NA	3.59 (2.64–4.88)	2.9	16.0	0.35–30.6	56	NA	NE	NE	13.7	0.48–23.5
Mass adjusted for b.w., μg kg^{-1}	72	NA	0.040 (0.030–0.054)	2.8	0.17	0.004–0.33	56	NA	NE	NE	0.13	0.008–0.24

b.w. = body weight; conc. = concentration; NA = not applicable; NE = not estimated.

[a]THPI LOD = 1.7 μg l^{-1}.

[b]The GM, GSD and 95% CI were estimated using MLE via PROC NLMIXED with person treated as a random effect. The data were left censored at the LOD. The log-normal distribution was specified in the model. Use of MLE for treating left-censored data was not feasible for the 24-h urine measures because several samples had been summed to create the 24-h value; instead, values below the LOD were replaced with LOD/2, the samples summed and the GM, GSD and 95% CI estimated via PROC MIXED with person treated as a random effect.

[c]Includes overnight urine.

[d]The percentage of days where all samples comprising the summed 24-h total had TPHI levels below the LOD was 24% for air blast and 55% for hand spray.

*$P < 0.05$ air blast compared to hand spray; **$P < 0.01$ air blast compared to hand spray; ***$P < 0.001$ air blast compared to hand spray.

Table 3. Pearson correlation matrix for air, hand, selected patch and urine exposure measures[a,b,c] (n, r, P-value)

	Captan						THPI in urine	
	Air (μg m^{-3})	Hand (μg)	R thigh (μg)	L thigh (μg)	R forearm (μg)	L forearm (μg)	24-h conc. (μg l^{-1})	24-h mass (μg)
Air (μg m^{-3})	1.0	140	138	136	139	140	127	127
		0.29	0.31	0.24	0.37	0.35	0.36	0.35
		0.0005	0.0002	0.0044	<0.0001	<0.0001	<0.0001	<0.0001
Hand (μg)		1.0	140	138	141	142	129	129
			0.32	0.36	0.39	0.52	0.62	0.57
			0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
R thigh (μg)			1.0	138	140	141	127	127
				0.84	0.60	0.58	0.40	0.35
				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
L thigh (μg)				1.0	138	139	126	126
					0.51	0.62	0.42	0.37
					<0.0001	<0.0001	<0.0001	<0.0001
R forearm (μg)					1.0	142	128	128
						0.80	0.53	0.51
						<0.0001	<0.0001	<0.0001
L forearm (μg)						1.0	129	129
							0.53	0.53
							<0.0001	<0.0001
24-h conc. (μg l^{-1})							1.0	130
								0.93
								<0.0001
24-h mass (μg)								1.0

Conc. = concentration; R = right; L = left.
[a]All exposure measures were log-transformed.
[b]All results remained significant when Spearman's correlation test was used.
[c]A mixed model approach using MLE for left-censored data was not feasible for these correlation analyses; instead, LOD/2 was imputed for data below the LOD and independence of observations was assumed.

Table 4. Frequency of [PPE] scores by mixing and applying

Score	Mixing, n = 139, no. (%)	Applying, n = 144, no. (%)
1.0	28 (20.1)	36 (25)
0.8	10 (7.2)	10 (6.9)
0.7	2 (1.4)	3 (2.1)
0.6	18 (13)	9 (6.2)
0.5	7 (5.0)	13 (9.0)
0.4	26 (18.7)	22 (15.3)
0.3	17 (12.2)	14 (9.7)
0.1	31 (22.3)	37 (25.7)

n = number of days.

completed spraying before or after 12:00, separately. Results were essentially unchanged (data not shown). When the algorithm components [MIX], [REPAIR] and [PPE] were examined together in mixed models, [PPE] was significantly associated with decreased exposure to the right and left thighs (P = 0.0003 and P = 0.008, respectively) and marginally associated with decreased exposure to the hand and left forearm (P = 0.08 and P = 0.05, respectively) (Table 6). [REPAIR] was marginally associated with increased left forearm exposure (P = 0.09) (Table 6). [MIX] was not significant for any exposure measure examined.

DISCUSSION

Applicators who hand sprayed captan in orchards had a distinctly different exposure distribution than applicators using air blast sprayers. For most external and for all biological exposure measures, captan and its metabolite THPI were detected more frequently among air blast applicators than among hand spray applicators. This exposure difference between hand spray and air blast application has implications for the AHS pesticide exposure intensity algorithm. While the AHS algorithm was significantly associated with captan exposures to the thighs, and marginally associated with forearm exposures, the algorithm was not associated with captan air, hand

Table 5. Regression coefficients (β) and *P*-values for mixed-effects models of the AHS algorithm score (independent variable) and each of the captan exposure measures (dependent variables)

Exposure measure	*n*	% ≥LOD	Algorithm score	
			B[a]	*P*-value
Captan				
Air, μg m^{-3}	141	48.2	0.004	0.89
Hand, μg	143	54.6	0.059	0.11
R thigh, μg	141	47.5	0.165	0.0003
L thigh, μg	139	43.9	0.132	0.0084
R forearm, μg	142	50.7	0.071	0.08
L forearm, μg	143	44.8	0.07	0.099
THPI				
24-h conc., μg l^{-1}	130	NA[b]	0.0001	1.0
24-h mass, μg	130	NA	−0.0035	0.84
Mass, first-morning Day 1, μg	140	61.4	−0.011	0.63
Excretion rate, overnight (Day 0 to Day 1), μg h^{-1}	117	59.8	−0.015	0.56

Conc. = concentration; NA = not applicable; R = right; L = left.
[a]The regression coefficient (β) and *P*-value were estimated using MLE via PROC NLMIXED with person treated as a random effect. The data were left censored at the LOD. The log-normal distribution was specified in the model. Use of MLE for treating censored data was not feasible for the 24-h urine measures because several samples had been summed to create the 24-h value; instead, values below the LOD were replaced with LOD/2, the samples summed and the β and *P*-value estimated via PROC MIXED with person treated as a random effect.
[b]The percentage of days where all samples comprising the summed 24-h total had TPHI levels below the LOD was 24% for air blast and 55% for hand spray.

rinse or urinary THPI levels. [PPE] was the only algorithm component associated with (decreased) exposure. The exposure distribution differences observed between air blast and hand spray suggest that the algorithm's current equal weighting of these two application methods may be contributing to the weak or absent associations.

Algorithm exposure weights were derived from sources with only external exposure data (i.e. dermal and air) (Dosemeci *et al.*, 2002). Additional factors affecting uptake and metabolism may be important for biological exposure measures. Air and dermal exposures may also have different exposure determinants, and the lack of agreement between the algorithm and the captan air data may indicate that a modified algorithm is needed to better estimate inhalation pesticide exposure intensity. Also, for applicators wearing a respirator, the algorithm would not be expected to agree well with measured air exposures as wearing a respirator, which is included in the [PPE] score, does not affect the amount of captan on the external sampling device. Although the algorithm does not adjust for the amount of chemical used in a day, we found that the amount of captan used, captan tank mix concentration, number of acres sprayed, duration of mixing and number of tank mixes were significantly higher for air blast than for hand spray, and duration of application was marginally higher for air blast as compared to hand spray (Hines *et al.*, 2007). Therefore, application method may be a proxy for these extent-of-use variables.

While use of a biomarker to evaluate the algorithm may seem preferable to external exposure measures (i.e. the assumption being that the biomarker indicates actual captan uptake), algorithm agreement with the biomarker could be affected by timing and completeness of sample collection, inter- and intraindividual variability in metabolism and/or exposure to captan on days immediately prior to urine collection. In separate analyses, we included the creatinine-corrected pre-application THPI urine concentration as an independent variable in the mixed models. While the pre-application concentration was highly significant in all models ($P < 0.001$), [MIX], [REPAIR] and [PPE] remained non-significant in each (data not shown). In future analyses, we will explore the influence of specific types of PPE on exposure levels, as well as other factors that may affect algorithm correlation with the various exposure measures.

The AHS algorithm has been previously evaluated against actual exposure measurements in urine (Coble *et al.*, 2005; Aquavella *et al.*, 2006). Among herbicide applicators, the algorithm correlated reasonably well with 2,4-D (2,4-dichlorophenoxyacetic acid) and less well for 4-chloro-2-methylphenoxyacetic acid (Coble *et al.*, 2005). Similarly, Aquavella

Table 6. Regression coefficients and *P*-values [β (*P*)] for mixed-effects models of the algorithm components [MIX], [REPAIR] and [PPE] (independent variables) and each of the captan exposure measures (dependent variables)[a]

	Dependent variables[b]									
	Captan						THPI			
Independent variables[c]	Air	Hand	R thigh	L thigh	R forearm	L forearm	Conc., 24 h	Mass, 24 h	Mass, first-morning Day 1	Excretion rate, overnight (Day 0 to Day 1)
n	141	143	141	139	142	143	130	130	140	117
% > LOD	48.2	54.6	47.5	43.9	50.7	44.8	NA	NA	61.4	59.8
[MIX] (0 or 9)[d]	1.56 (0.14)	−0.52 (0.62)	0.19 (0.86)	−1.07 (0.40)	−0.15 (0.90)	−1.47 (0.20)	−0.35 (0.48)	−0.09 (0.86)	−0.13 (0.85)	−0.02 (0.98)
[REPAIR] (0 or 2)	0.14 (0.69)	0.21 (0.58)	−0.26 (0.51)	0.45 (0.37)	0.64 (0.15)	0.78 (0.09)	0.02 (0.9)	0.06 (0.73)	0.06 (0.82)	0.17 (0.55)
[PPE] (0.1–1.0)	0.11[e] (0.84)	1.32 (0.08)	3.53 **(0.0003)**[f]	2.74 **(0.008)**	1.17 (0.14)	1.69 (0.05)	0.058 (0.86)	−0.10 (0.78)	−0.20 (0.67)	−0.44 (0.39)

β = regression coefficient; *n* = number of days; NA = not applicable; R = right; L = left.

[a]The regression coefficient (β) and *P*-value were estimated using MLE via the NLMIXED procedure in SAS with person treated as a random effect. The data were left censored at the LOD. The log-normal distribution was specified in the model. Use of MLE for treating censored data was not feasible for the 24-h urine measures because several samples had been summed to create the 24-h value; instead, values below the LOD were replaced with LOD/2 and the β and *P*-value estimated via the MIXED procedure in SAS with person treated as a random effect.

[b]Dependent variables were log transformed.

[c][MIX] and [REPAIR] scores were entered as categorical variables in the model with the lower category as the reference value. [PPE] score was entered as a continuous variable. Worker was treated as a random effect and a compound symmetric covariance structure was used.

[d]A [MIX] score of 6 was included in the nine categories. No participant had a [MIX] score of 3.

[e]A higher [PPE] score indicates less use of personal protective equipment. Therefore, a positive β for [PPE] indicates that as a person uses less personal protective equipment, the exposure increases.

[f]Values in bold are statistically significant at $\alpha = 0.05$.

et al. (2006) found modest correlations between the algorithm and liquid formulations of glyphosate, 2,4-D and chlorpyrifos when field observers assessed application conditions and PPE; however, correlation was lacking for granular chlorpyrifos applications. Captan was always applied as a water-based liquid in our study. The two aforementioned algorithm evaluations did not include air blast; only boom spray, in-furrow application and hand spray.

Overall, our data suggest that algorithm exposure weights for air blast and hand spray should be re-evaluated, with a higher weight possibly being assigned to air blast relative to hand spray. In a preliminary examination of the algorithm in which the score for hand spray was decreased to 0 and the score for air blast was increased to 10 (extremes of the scale), *P*-values decreased for all exposure measures, with hand rinse captan becoming significant ($P = 0.01$) and the 24-h THPI concentration approaching significance ($P = 0.09$) (data not shown). This suggests that an AHS algorithm with a revised [APPLY] component for air blast relative to hand spray would improve the algorithm's exposure classification reliability.

Studies comparing pesticide exposures from air blast and hand spray applications in orchards are few. In separate studies in citrus orchards, ethion exposures of two handgun mixer-applicators were approximately eight times higher than dicofol exposures of two air blast applicators (Nigg *et al.*, 1986; Nigg *et al.*, 1990). However, we found higher captan exposure among air blast than among hand spray applicators. Our finding may be related to the larger amounts of captan sprayed by air blast than by hand spray (Hines *et al.* 2007).

Captan was detected most frequently on the hands, forearms and thighs in our study. This pattern suggests that elbow-length chemically resistant gloves and a chemically resistant apron or garment that protects the upper legs might reduce exposures during captan application in orchards. GM hand exposures among Dutch reentry workers using 50% ethanol rinses were ~20% lower than our applicator exposures (7.7 versus 9.7 mg m^{-2} per hour; NIOSH estimate based on a GM of 540 μg per hand, 360 cm^2 per hand and a GM application time of 93 min) (Fiserova-Bergerova, 1993; de Cock *et al.*, 1998). Different solvent removal efficiencies might partly explain exposure differences.

Early studies of orchard applicators indicated that inhalation, as measured by respirator pads, was a possible route of captan exposure (Oudibier *et al.*, 1974; Hansen *et al.*, 1978; McJilton *et al.*, 1983). More recently, Dutch orchard farmers had a GM captan air exposure ~20% lower than our applicators (22.6 versus 29 μg m^{-3}) (de Cock *et al.*, 1998). THPI measured in the first 24-h urine sample of 14 of these Dutch farmers, however, was ~2-fold higher than in our applicators (7.8 versus 3.59 μg) (de Cock *et al.*, 1995). Our higher air levels may be related to low use of tractors with cabs (17% NIOSH versus 52% Dutch), while higher Dutch urine levels may be related to more extensive captan use and longer air blast spray times than in our study. For example, our mean duration of application was 2-fold lower than the Dutch study (93 versus 211 min), our mean amount of captan applied was 20% less (7.9 versus 10.4 kg) and our mean number of acres sprayed was 2.8-fold lower (5.3 versus 14.8).

THPI levels have also been reported in non-orchard crops. Applicators applying captan to grapes had mean THPI concentrations in two post-application spot urine samples ranging from <LOD to 35 μg l^{-1} (Winterlin *et al.*, 1986). This range is similar to our study, although these applicators applied ~30% more captan (11 versus 7.9 kg) than our applicators. THPI was not detected in the urine of applicators applying captan to strawberries; however, the study LOD was high (30 μg l^{-1}) (Winterlin *et al.*, 1984). Mean THPI levels in strawberry harvesters (2–5.3 μg day^{-1}) were also comparable to our data (Krieger and Dinoff, 2000).

Urine samples were collected for only the first 24 h in our study. Although oral dosing studies with captan in humans have indicated that THPI is mostly eliminated within 24 h (Krieger and Thongsinthusak, 1993), de Cock *et al.* (1995) found that THPI continued to be excreted up to 48 h in captan-exposed orchard applicators. For the purposes of identifying exposure determinants, de Cock *et al.* (1995) also found that the 24-h and 48-h samples gave comparable results; however, urine collection compliance was poorer for the 48-h sample. Thus, our THPI levels most likely underestimate the applicators' full captan exposure, although, as shown by de Cock, the data are useful for assessing exposure (algorithm) determinants.

THPI was detected in pre-application urine samples 32 and 14% of the time for air blast and hand spray, respectively, even though applicators applied captan only 8% of the time in the 2 days before urine collection. Applicators also rarely entered orchards that had been sprayed with captan in the 7 days prior to urine collection. Captan residues have been found on food and food products (Newsome *et al.*, 2000); however, it is unknown if dietary captan contributed to THPI levels in our applicator urine samples.

Major strengths of this study are its large sample size and the inclusion of a substantial number of applicators who hand sprayed, allowing for comparisons to air blast application. The GC/MS analysis also captured the captan degradate, THPI. The use

of MLE to treat left-censored data among air blast users allowed us to obtain asymptotically unbiased estimates (assuming a log-normal distribution); however, the severe censoring among hand spray users (i.e. >50%) was a limitation in obtaining accurate exposure estimates for this group. Dermal exposure monitoring was conducted concurrently with biomonitoring which could have reduced the captan available for uptake. To lessen this impact, total patch surface area was kept small and only one hand was rinsed.

CONCLUSION

AHS private applicators using air blast sprayers in orchards generally had higher captan exposures than those who hand sprayed. Captan was detected in personal breathing-zone samples on >60% of the days that it was applied by air blast. This frequency of airborne detection together with the significant correlations seen between external and internal exposure measures indicate exposure of these orchard applicators to captan by both dermal and inhalation routes with eventual uptake into the body. The AHS pesticide exposure intensity algorithm, while significantly and marginally predictive of thigh and forearm exposures, respectively, did not predict air, hand rinse or urinary THPI exposures. This lack of association may be due, in part, to the assignment of equal exposure weights to air blast and hand spray application methods in the AHS algorithm, as well as to factors not captured by the algorithm, such as exposure to captan on days immediately prior to sampling (especially for the biomarker). We recommend that the algorithm exposure weights of the two application methods be reevaluated.

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APPENDIX 1

AHS pesticide exposure intensity algorithm

Exposure intensity score
= (MIX + APPLY + REPAIR) × PPE.

MIX:
if [MIX] = never mixed, then score = 0
if [MIX] = <50% of the time mixed, then score = 3
if [MIX] = 50% + of the time mixed , then score = 9

APPLY for Fungicides:
if [APPLY] = does not apply, then score = 0
if [APPLY] = aerial-aircraft, then score = 1
if [APPLY] = in furrow/banded, then score = 2
if [APPLY] = boom on tractor, then score = 3
if [APPLY] = backpack, then score = 8
if [APPLY] = hand spray, then score = 9
if [APPLY] = air blast, then score = 9
if [APPLY] = mist blower/fogger, then score = 9

REPAIR:
if [REPAIR] = Does not repair, then score = 0
if [REPAIR] = Repair, then score = 2

PPE:
if [PPE] = never used, then PPE 0 = Yes
if [PPE] = face shield or goggles, then PPE 1 = Yes
if [PPE] = fabric or leather gloves, then PPE 1 = Yes
if [PPE] = other protective clothing, such as boots, then PPE 1 = Yes
if [PPE] = cartridge respirator or gas mask, then PPE 2 = Yes
if [PPE] = disposable outer clothing, then PPE 2 = Yes
if [PPE] = chemically-resistant rubber gloves, then PPE 3 = Yes

PPE 0	PPE 1	PPE 2	PPE 3	PPE reduction score
Yes	No	No	No	1.0
No	Yes	No	No	0.8
No	No	Yes	No	0.7
No	No	No	Yes	0.6
No	Yes	Yes	No	0.5
No	Yes	No	Yes	0.4
No	No	Yes	Yes	0.3
No	Yes	Yes	Yes	0.1

APPENDIX 2

Results of laboratory and field QC samples

Matrix: analyte	*n*	Fortification or measured level range[a]	Mean recovery (%)	Pooled RSD (%)
Urine: THPI				
Laboratory fortified	179	5–40 μg l^{-1}	86	9.1
NIOSH fortified[b]	45	5–25 μg l^{-1}	80	13
Field duplicates > LOD[c]	65	2.0–31 μg l^{-1}	NA	8.1
Field duplicates > LOQ[d]	35	5.1–31 μg l^{-1}	NA	4.9
Urine: creatinine				
Laboratory	31	1 g l^{-1}	94	7.3
Field duplicates	141	0.25–3.0 g l^{-1}	NA	5.9
Air: captan				
Laboratory fortified	34	60–405 μg	92	6.6
NIOSH fortified[e]				
Not exposed to field ambient conditions	54	58–400 μg	89	13
Exposed to field ambient conditions	54	58–400 μg	88	10
Hand: captan				
Laboratory fortified	28	24–34200 μg	101	6.7
NIOSH fortified[e]				
Not exposed to field ambient conditions[f,g]	51	3700–34000 μg	104	5.4
Patch: captan				
Laboratory fortified	134	350–1220 μg	95	10
NIOSH fortified[e]				
Not exposed to field ambient conditions[h]	54	340–1200 μg	96	13
Exposed to field ambient conditions[h]	54	340–1200 μg	102	15
Hand: thiophanate-methyl				
Laboratory fortified	28	25–45000 μg	101	8.2
NIOSH fortified[e]				
Not exposed to field ambient conditions[i]	51	3700–4600 μg	101	9.0
Hand: carbendazim				
Laboratory fortified	28	21–19900 μg	105	7.5
NIOSH fortified[e]				
Not exposed to field ambient coditions[j]	51	2300–19000 μg	105	8.9

NA = not applicable.
[a]Fortification level for laboratory- and NIOSH-fortified samples.
[b]All blanks were non-detectable (ND).
[c]Duplicate pairs where both samples greater than the LOD.
[d]Duplicate pairs where both samples greater than the LOQ.
[e]All not-exposed blanks ($n = 18$) were ND. One out of 18 exposed blanks was between the LOD and LOQ.
[f]All blanks ($n = 18$) were ND.
[g]No exposed hand samples, as the hand rinse was taken at end of application and therefore not exposed to field ambient conditions.
[h]All not-exposed ($n = 18$) and exposed ($n = 18$) blanks were ND.
[i]All blanks ($n = 18$) were ND.
[j]All blanks (n=18) were ND.

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