

Determinants of Captan Air and Dermal Exposures among Orchard Pesticide Applicators in the Agricultural Health Study

CYNTHIA J. HINES^{1*}, JAMES A. DEDDENS^{1,2}, JOSEPH COBLE³,
FREYA KAMEL⁴ and MICHAEL C. R. ALAVANJA³

¹National Institute for Occupational Safety and Health, 4676 Columbia Pkwy, R-14, Cincinnati, OH 45226, USA; ²Department of Mathematical Sciences, University of Cincinnati, PO Box 21025, Cincinnati, OH 45221, USA; ³National Cancer Institute, 6120 Executive Boulevard, Rockville, MD 20892, USA; ⁴National Institute of Environmental Health Sciences, 111 TW Alexander Drive, Research Triangle Park, NC 27709, USA

Received 3 February 2010; in final form 19 January 2011; published online 22 March 2011

Objectives: To identify and quantify determinants of captan exposure among 74 private orchard pesticide applicators in the Agricultural Health Study (AHS). To adjust an algorithm used for estimating pesticide exposure intensity in the AHS based on these determinants and to compare the correlation of the adjusted and unadjusted algorithms with urinary captan metabolite levels.

Methods: External exposure metrics included personal air, hand rinse, and dermal patch samples collected from each applicator on 2 days in 2002–2003. A 24-h urine sample was also collected. Exposure determinants were identified for each external metric using multiple linear regression models via the NLMIXED procedure in SAS. The AHS algorithm was adjusted, consistent with the identified determinants. Mixed-effect models were used to evaluate the correlation between the adjusted and unadjusted algorithm and urinary captan metabolite levels.

Results: Consistent determinants of captan exposure were a measure of application size (kilogram of captan sprayed or application method), wearing chemical-resistant (CR) gloves and/or a coverall/suit, repairing spray equipment, and product formulation. Application by airblast was associated with a 4- to 5-fold increase in exposure as compared to hand spray. Exposure reduction to the hands, right thigh, and left forearm from wearing CR gloves averaged ~80%, to the right and left thighs and right forearm from wearing a coverall/suit by ~70%. Applicators using wettable powder formulations had significantly higher air, thigh, and forearm exposures than those using liquid formulations. Application method weights in the AHS algorithm were adjusted to nine for airblast and two for hand spray; protective equipment reduction factors were adjusted to 0.2 (CR gloves), 0.3 (coverall/suit), and 0.1 (both).

Conclusions: Adjustment of application method, CR glove, and coverall weights in the AHS algorithm based on our exposure determinant findings substantially improved the correlation between the AHS algorithm and urinary metabolite levels.

Keywords: agriculture; captan; dermal exposure—pesticides, determinants of exposure; exposure assessment—mixed models; orchards; pesticide exposure; variance components

INTRODUCTION

Identifying determinants of pesticide exposure in agriculture is of considerable interest for exposure assess-

ment in epidemiological studies. To a large extent, the exposure scenario and population of interest dictate the exposure determinants found for a group of workers. For example, exposure mechanisms experienced by applicators (e.g. mixing, loading, applying, equipment repair, cleaning) can be quite different than those experienced by field re-entry workers (e.g.

*Author to whom correspondence should be addressed.
Tel: 1-513-841-4453; fax: 1-513-841-4456;
e-mail: chines@cdc.gov

dislodgeable foliar residues) (de Cock *et al.*, 1998). Even among applicators, exposure determinants may differ for private and commercial applicators due to differences in the amount and duration of spraying and methods used for spraying and mixing. This variability in tasks, equipment, and behavior among agricultural workers ultimately influences the shape of exposure distributions.

In exposure–response analyses, it is important to evaluate a wide range of exposures and to accurately identify participants at the high and low ends of the exposure distribution. Exposure assessment approaches in cohort studies that rely on number of years and number of days per year of pesticide application as surrogate measures of pesticide exposure assume that exposure intensity is similar for applicators who have the same frequency and duration of exposure. This assumption of equal exposure intensity, while practical for large cohort studies, may introduce exposure misclassification as exposure intensity is likely to vary among applicators due to differences in their exposure modifying factors. Numerous studies have shown the importance of factors that modify pesticide exposure intensity, such as personal protective equipment (PPE) used, application method, and formulation (de Cock *et al.*, 1998; Stewart *et al.*, 1999; Hines *et al.*, 2001; Arbuckle *et al.*, 2002; Harris *et al.*, 2002; Acquavella *et al.*, 2004; Geer *et al.*, 2004; Alexander *et al.*, 2006, 2007; Baldi *et al.*, 2006; Bakke *et al.*, 2009; Lebailly *et al.*, 2009; Thomas *et al.*, 2010a). Identifying and quantifying the important determinants of exposure for study participants can minimize exposure misclassification by improving the exposure contrast between individuals and by better identifying the highest-exposed individuals.

Differences in pesticide exposure intensity among applicators were addressed in the Agricultural Health Study (AHS) by developing an algorithm to estimate pesticide exposure intensity (Dosemeci *et al.*, 2002). The AHS is a cohort of 57 310 licensed private and commercial pesticide applicators and 32 346 spouses of the private applicators enrolled from 1993 to 1997 in Iowa and North Carolina (Alavanja *et al.*, 1996). The algorithm contains four components thought to be important determinants of pesticide exposure intensity: (i) application method, (ii) personally mixing pesticides, (iii) repairing spray equipment, and (iv) wearing PPE. Another consideration in selecting algorithm determinants was the likelihood that AHS participants could reliably provide information on these determinants over their lifetime use of pesticides.

Post-enrollment field studies in the AHS (Hines *et al.*, 2008; Thomas *et al.*, 2010b) along with data

from a Canadian study of applicator pesticide exposure (Arbuckle *et al.*, 2002; Coble *et al.*, 2005) and the Farm Family Exposure Study in Minnesota and South Carolina (Acquavella *et al.*, 2006) have been used to evaluate the performance of the algorithm. Findings from such evaluation studies could be used to support revisions to the algorithm to improve pesticide exposure intensity estimates. In a previous analysis of captan exposure data collected from AHS orchard applicators (Hines *et al.*, 2008), we found that while the AHS algorithm significantly predicted captan exposure to the thighs, the algorithm did not predict captan exposure to the hands, other body locations, air, or urinary metabolite levels. In this analysis, we use air, hand, and dermal patch exposure data collected from the AHS orchard applicators to identify important determinants of captan exposure, adjust the AHS algorithm based on the identified determinants, and then evaluate the correlation between the adjusted algorithm and urinary biomarker levels.

METHODS

Study population

A total of 74 private pesticide applicators enrolled in the AHS who grew apples and/or peaches in Iowa ($n = 21$) or North Carolina ($n = 53$) were recruited for this study in 2002–2003. Recruitment procedures and applicator characteristics have been previously described (Hines *et al.*, 2007). All 74 applicators applied the fungicide captan to tree fruit. Captan was used as a marker of fungicide exposure. Participation was voluntary and informed consent was obtained. This study was approved by all appropriate Institutional Review Boards.

Sample collection and analysis

All but 4 of the 74 applicators were sampled on 2 days (usually in the same year) at least 7 days apart; the remaining four applicators were sampled on 1 day each, for a total of 144 monitored days. A personal breathing zone air sample, 10 dermal patches (worn under protective clothing if used), and a hand rinse sample of one hand were collected from each applicator on each sampled day. Applicators also collected all urine starting with that day's first-morning void (Day 0) through the first-morning void of the next day (Day 1), collected in five timed periods. Details of sampling and analytical procedures are provided in Hines *et al.* (2008).

Briefly, air samples were collected at 1 l.p.m. on XAD-2 OSHA Versatile Samplers (OVS) with quartz pre-filters. Patch samplers consisting of a 10×10 cm piece of Texwipe® Alpha Wipe® polyester clean

room wipe in a holder with a 7.6-cm diameter circle cut in one side (45.4 cm² sampling area) were attached to clothing or skin at 10 body locations (right thigh, left thigh, right lower leg, left lower leg, right forearm, left forearm, right shoulder, left shoulder, chest, and back). Air and patch samples were collected for the duration of pesticide handling activities (Hines *et al.*, 2007). After completing all pesticide handling activities, a hand rinse was performed in 150 ml of isopropanol on the dominant hand (except for hand spray where the hand holding the wand was sampled). Only one hand was rinsed to minimize interference with concurrent urinary metabolite biomonitoring. Captan was determined in air, hand rinse, and dermal patch samples by high-performance liquid chromatography with confirmation by gas chromatography/mass spectrometry according to NIOSH methods 5606, 9202, 9205, and 9208 (NIOSH, 2003). A metabolite of captan, *cis*-1,2,3,6-tetrahydrophthalimide (THPI), was determined in urine by gas chromatography–mass spectrometry.

Statistical analysis

Exposure data were highly right skewed (approximating a log-normal distribution) and a natural log transformation was applied. Summary statistics, including geometric mean (GM) and geometric standard deviation (GSD), were computed for air, hand, and patch locations using maximum likelihood estimation (MLE) via the NLMIXED procedure in SAS v. 9.1 (Cary, NC, USA) to account for left-censoring (i.e. data below the limit of detection) and repeated measurements on workers (Thiébaud *et al.*, 2006; Jin *et al.*, 2011).

Covariate data pertaining to participant demographics, application size, mixing and application practices, PPE use, cleaning and repair of spray equipment, hygiene practices, and ambient conditions were initially examined for number of missing values, number of observations per category, and plausibility of a relationship to one or more of the dependent variables based on either literature support or subject matter expertise (i.e. occupational hygienists experienced in pesticide exposure assessment). Dichotomous covariates with <10 observations in a response category were not included in regression analyses, except for the covariate ‘high pesticide exposure event’ ($n = 8$) because of a strong *a priori* interest in this covariate (Alavanja *et al.*, 1999). This review process resulted in 29 covariates (dichotomous and continuous) in the regression analyses. These covariates were grouped into six categories: demographic ($n = 3$), application size ($n = 4$), mixing ($n = 6$), applying ($n = 10$), equipment clean-

ing ($n = 3$), and ambient conditions ($n = 3$). Pearson’s coefficient was used to examine the correlation among four application size covariates (kilogram of captan active ingredient (a.i.) applied, duration of application, number of acres sprayed, and number of tank mixes) and two other covariates also suspected to be related to application size (application method and tractor use), for a total of six ‘application size-related’ covariates. A natural log transformation was applied to kilogram of captan a.i. applied, duration of application, and number of acres sprayed because these data were skewed to the right.

Regression modeling was performed using the NLMIXED procedure in SAS. Air, hand, and the four patch locations with the highest captan detection frequency were treated as dependent variables. MLE was used in all models due to left-censoring in the dependent variable. Univariate regression models were run for each exposure metric and all covariates. *P*-values were not adjusted for multiple comparisons. Multiple regression models were constructed via a stepwise forward selection procedure with inclusion at $P \leq 0.025$ (selected to obtain a more parsimonious model). The initial step included a single ‘application size-related’ covariate (i.e. kilogram captan a.i. applied), selected on strength of association in the univariate analyses, plus the remaining 23 covariates. Multiple regression models were re-run with application method as the ‘application size-related’ covariate because kilogram captan a.i. applied is not used in the AHS algorithm. Of the six application size-related variables, application method is the only one used in the AHS algorithm. Results from multiple regression models with application method were used to modify the AHS algorithm. A previously published analysis examining the association between the algorithm and urinary THPI levels (Hines *et al.*, 2008) was re-run (using the PROC NLMIXED procedure in SAS), except the adjusted algorithm was used.

Total variance was estimated by fitting a model containing worker only as a random effect. In the final multiple regression models, within- and between-worker variances were estimated from the random effects portion of the model and the percentage of the total variance explained by the fixed effects was determined by subtracting the sum of the within- and between-worker variances from the total variance (worker-only model).

RESULTS

Captan levels in air, hand rinse, and patch samples are summarized in Table 1. Captan detection

frequencies and GMs were somewhat higher for the right side as compared to the left side of the body, perhaps because 89% of the applicators were right-handed. Significant correlation was found among covariates related to application size, with associations strongest among kilogram captan a.i. applied, number of acres sprayed, and application method (Table 2). Covariates identified as potentially significant exposure modifiers in univariate regression models (Table 3) were generally significant for one or more exposure metrics in multiple regression models (Tables 4–5).

Exposure determinants—models with kilogram captan a.i. applied

Our initial set of models was developed to identify the strongest predictors of captan exposure

(Table 4). Kilogram of captan a.i. applied was a significant exposure determinant for all metrics evaluated. Formulation was an important exposure determinant for four (air, right and left thigh, and right forearm) of the six metrics, with a wettable powder formulation associated with significantly higher captan exposures than a liquid formulation. Use of chemical-resistant (CR) gloves significantly reduced captan exposure to the hands (77% = $(1 - \exp(0.23)) \times 100$) and left forearm (82%) when worn while mixing and to the right thigh (68%) when worn while applying. Wearing a coverall/spray suit while mixing significantly reduced exposures to the right and left thighs (75 and 89%, respectively) and to the right forearm (76%). Wearing both a coverall/spray suit

Table 1. Summary of captan levels in air, hand rinse, and patch samples

	<i>n</i>	% ≥ LOD ^a	GM ^b (95%CI)	GSD	95th Percentile	Range of values > LOD
Air (µg m ⁻³)	141	48.2	18 (12–26)	4.8	230	7.9–1500
Hand (µg)	143	54.6	230 (130–380)	9.0	6300	75–12000
R. thigh (µg)	141	47.5	24 (11–53)	17	2000	15–9300
L. thigh (µg)	139	43.9	21 (9.5–46)	18	2300	20–4500
R. forearm (µg)	142	50.7	31 (18–54)	9.9	1700	15–6000
L. forearm (µg)	143	44.8	22 (12–42)	11	890	15–5400
R. lower leg (µg)	133	33.1	8.9 (3.4–23)	21	1500	15–7000
L. lower leg (µg)	134	30.6	7.1 (2.8–18)	15	860	13–2500
R. shoulder (µg)	142	32.4	11 (5.2–22)	10	430	18–2200
L. shoulder (µg)	141	32.6	9.9 (4.3–23)	14	490	17–5400
Chest (µg)	141	33.3	10 (5.0–21)	10	490	13–3400
Back (µg)	142	24.6	4.9 (1.8–14)	12	240	14–2600

n, number of days; R, right; L, left; LOD, limit of detection.

^aLODs = air: 0.4–2 µg per sample; hand: 30–20 µg per sample; and patches: 6–30 µg per sample.

^bGM, GSD, and 95% confidence interval (CI) were estimated using maximum likelihood estimation 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.

Table 2. Pearson’s correlation matrix^a for covariates correlated with application size, *r* (*P*-value), *n* = 144

	Ln(captan a.i. applied, kg)	Ln(number of acres sprayed)	Ln(duration applied, min)	Number of tank mixes applied	Application method	Tractor used
Ln(captan a.i. applied, kg)	1.0	0.76 (<0.0001)	0.62 (<0.0001)	0.37 (<0.0001)	0.77 (<0.0001)	0.59 (<0.0001)
Ln(number of acres sprayed)		1.0	0.66 (<0.0001)	0.40 (<0.0001)	0.54 (<0.0001)	0.37 (<0.0001)
Ln(duration applied, min)			1.0	0.51 (<0.0001)	0.22 (0.0076)	0.17 (0.048)
Number of tank mixes applied				1.0	0.22 (0.0070)	0.039 (0.64)
Application method					1.0	NA ^b (<0.0001)
Tractor used						1.0

NA, not applicable.

^aObservations were treated as independent.

^bAs both variables are dichotomous, a chi-square *P*-value is reported.

Table 3. Univariate linear regression results for captan in air, hand rinse, and patch samples

Covariate	Air (<i>n</i> = 141)		Hand (<i>n</i> = 143)		R. thigh (<i>n</i> = 141)		L. thigh (<i>n</i> = 139)		R. forearm (<i>n</i> = 142)		L. forearm (<i>n</i> = 143)	
	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value
	ln(captan., $\mu\text{g m}^{-3}$)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)	
Demographic^a												
Age, years (median = 62.5)	-0.037	0.013	0.0192	0.37	0.0097	0.74	0.0252	0.39	-0.0174	0.42	-0.016	0.51
Number years applied fungicides (median = 22)	0.0027	0.84	0.0189	0.29	0.0413	0.096	0.0529	0.038	0.0255	0.16	0.0317	0.11
Education, more than high school (<i>n</i> = 52)	-0.532	0.18	-0.766	0.17	-0.485	0.55	-1.134	0.16	0.0361	0.95	-0.345	0.57
Application size												
Ln(captan a.i. applied, kg, median = 1.0)	0.519	<0.0001	0.491	<0.0001	0.598	<0.0001	0.488	0.0097	0.550	<0.0001	0.646	<0.0001
Ln(number of acres sprayed, median = 3)	0.632	0.0001	0.511	0.003	0.820	<0.0001	0.648	0.012	0.695	0.0003	0.820	<0.0001
Ln(duration applied, min, median = 76)	0.746	0.005	0.543	0.022	0.977	<0.0001	1.542	0.0002	1.206	<0.0001	1.283	<0.0001
Number tank mixes applied (median = 1)	0.077	0.36	0.173	0.087	0.348	0.0007	0.427	0.003	0.420	0.0002	0.386	0.0006
Mixing												
WP formulation (<i>n</i> = 117) (liquid = ref.)	2.915	0.0002	0.064	0.92	2.614	0.086	3.020	0.023	2.252	0.006	2.177	0.020
Mixed outdoors (<i>n</i> = 116) (shed = ref.)	-0.372	0.39	0.285	0.62	0.292	0.69	1.138	0.19	-0.324	0.61	0.431	0.55
Wore CR glove—mixing (<i>n</i> = 94)	-0.196	0.60	-1.490	0.0005	-1.581	0.024	-1.522	0.040	-0.642	0.25	-1.584	0.009
Wore overall/suit—mixing ^b (<i>n</i> = 69)	0.541	0.10	-0.204	0.60	-1.226	0.010	-2.030	0.0004	-1.161	0.016	-0.428	0.45
Mean captan conc. in tank, mg l ⁻¹ (median = 1.6)	0.272	0.008	0.411	0.004	0.300	0.083	0.165	0.39	0.188	0.22	0.181	0.26
Washed hands after mixing (<i>n</i> = 32)	-0.063	0.86	0.0008	1.0	0.0562	0.89	-0.343	0.54	-0.239	0.64	-0.835	0.13
Applying												
Used additive(s) ^c in tank mix (<i>n</i> = 47)	0.585	0.12	0.365	0.457	1.933	0.002	1.602	0.022	1.518	0.002	2.031	0.0002
AB application method (<i>n</i> = 79) (HS = ref.)	1.261	0.0006	1.797	0.0002	0.864	0.21	-0.071	0.92	0.772	0.14	1.312	0.019
Wore CR glove—applying (<i>n</i> = 85)	-0.252	0.48	-1.053	0.018	-1.802	0.0008	-1.344	0.028	-0.815	0.10	-0.963	0.068

Table 3. Continued

Covariate	Air (n = 141)		Hand (n = 143)		R. thigh (n = 141)		L. thigh (n = 139)		R. forearm (n = 142)		L. forearm (n = 143)	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
	ln(captan., $\mu\text{g m}^{-3}$)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)		ln(captan, μg)	
Wore coverall/suit—applying (n = 71)	0.372	0.26	-0.097	0.81	-0.873	0.10	-1.741	0.004	-1.074	0.026	-0.783	0.140
Tractor used (109)	1.222	0.006	1.148	0.058	0.633	0.45	0.020	0.98	0.135	0.83	0.838	0.23
Enclosed cab on tractor (n = 18)	0.641	0.22	0.350	0.62	1.315	0.18	0.343	0.74	0.602	0.43	0.661	0.42
Dust filter in cab (n = 12)	0.291	0.60	-0.515	0.44	1.024	0.17	-0.709	0.46	0.193	0.82	0.224	0.80
Late tree fruit stage (n = 101) (early = ref.) ^d	0.525	0.14	0.663	0.099	1.068	0.010	1.185	0.031	1.541	0.003	1.720	0.0007
Self-reported HPEE (n = 8)	-1.119	0.13	0.513	0.47	-0.637	0.46	0.133	0.90	-0.087	0.91	-1.50	0.11
Sprayed high density trees (n = 11)	-0.014	0.98	0.0063	0.99	-0.123	0.92	-0.173	0.89	0.0361	0.95	0.507	0.63
Equipment cleaning/repair												
Cleaned nozzles (n = 47)	0.0014	1.0	0.412	0.24	-0.0014	1.0	-0.653	0.14	-0.172	0.70	-0.802	0.071
Cleaned spray equipment (n = 67)	-0.318	0.30	-0.119	0.73	-0.566	0.13	-0.196	0.66	-0.387	0.37	-0.729	0.099
Repaired spray equipment (n = 26)	0.253	0.46	0.266	0.48	0.191	0.62	0.672	0.15	0.752	0.085	0.872	0.052
Ambient conditions												
Mean ambient temperature (°C) (median = 23.5)	0.027	0.24	-0.012	0.65	0.044	0.15	0.082	0.028	0.043	0.17	0.0026	0.94
Mean relative humidity (%) (median = 55)	-0.0084	0.29	0.0020	0.85	0.0068	0.52	0.0157	0.22	0.0019	0.88	0.0103	0.42
Mean wind speed (km h ⁻¹) (median = 2.8)	0.0078	0.85	0.0324	0.54	0.0445	0.39	0.0427	0.49	0.020	0.76	-0.0037	0.95

Bolded values are statistically significant (P < 0.05). AB, airblast; conc., concentration; HPEE, high pesticide exposure event; HS, hand spray; L, left; Liq, liquid; R, right; ref., referent; WP, wettable powder.

^aDemographic covariates N = 74, mixing covariates N = 139, and all other covariates N = 144.

^bIncludes fabric coveralls, disposable coveralls (e.g. Tyvek), and spray suits.

^cIncludes spreaders, stickers, surfactants, and defoamers.

^dEarly = dormancy to petal fall and late = fruit set to harvest.

Table 4. Multiple linear regression models for captan in air, hand rinse, thigh patch, and forearm patch samples: kilogram of captan a.i. applied included as the measure of application size

Dependent variable	<i>n</i>	β	SE	<i>P</i> -value	Factor ^a
Air: ln(captan, $\mu\text{g m}^{-3}$)					
Intercept	136	0.08075	0.6376	0.90	
Ln(captan a.i. applied, kg)		0.5356	0.08908	<0.0001	1.7
Captan formulation (WP/liquid = ref.)		3.0697	0.6345	<0.0001	22
Hand: ln(captan, μg)					
Intercept	138	6.5126	0.3026	<0.0001	
Ln(captan a.i. applied, kg)		0.4883	0.09940	<0.0001	1.6
Wore CR gloves—mixing (Y/N = ref.)		-1.4803	0.3631	0.0001	0.23
R. thigh: ln(captan, μg)					
Intercept	136	2.2940	0.9288	0.016	
Ln(captan a.i. applied, kg)		0.6183	0.1256	<0.0001	1.9
Wore coverall/suit—mixing (Y/N = ref.)		-1.3838	0.3919	0.0007	0.25
Wore CR gloves—applying (Y/N = ref.)		-1.400	0.4991	0.015	0.32
Captan formulation (WP/liquid = ref.)		2.6361	0.9516	0.0071	14
L. thigh: ln(captan, μg)					
Intercept	134	-2.6613	2.0842	0.2058	
Ln(captan a.i. applied, kg)		0.6078	0.1681	0.0006	1.8
Wore coverall/suit—mixing (Y/N = ref.)		-2.1989	0.4905	<0.0001	0.11
Captan formulation (WP/liquid = ref.)		2.8703	1.0235	0.0065	18
Age, years		0.06542	0.02657	0.016	1.1
Repair (Y/N = ref.)		1.1285	0.4488	0.0142	3.1
R. forearm: ln(captan, μg)					
Intercept	137	2.5367	0.6501	0.0002	
Ln(captan a.i. applied, kg)		0.5599	0.1172	<0.0001	1.8
Wore coverall/suit—mixing (Y/N = ref.)		-1.4281	0.4032	0.0007	0.24
Captan formulation (WP/liquid = ref.)		1.7532	0.6614	0.0099	5.8
Repair (Y/N = ref.)		0.9341	0.3946	0.0207	2.5
L. forearm: ln(captan, μg)					
Intercept	138	3.8769	0.4423	<0.0001	
Ln(captan a.i. applied, kg)		0.5940	0.1365	<0.0001	1.8
Wore CR gloves—mixing (Y/N = ref.)		-1.6996	0.4914	0.0009	0.18
Washed hands after mixing (Y/N = ref.)		-1.1111	0.3982	0.0068	0.33
Additive used (Y/N = ref.)		1.4087	0.5285	0.0095	4.1
Repair (Y/N = ref.)		0.8945	0.3436	0.0112	2.4

R, right; L, left; ref., referent; WP, wettable powder.

^aexp(β). Dichotomous variable: multiplicative factor by which captan exposure increases or decreases from reference condition. Continuous variable: multiplicative factor by which captan exposure increases (or decreases) when variable (e.g. kilogram of captan a.i) increases (or decreases) by a multiplicative factor of e (i.e. 1.7).

while mixing and CR gloves while applying reduced right thigh exposure by a combined 92%. Repairing spray equipment during the monitored period was associated with increased captan exposure for three (left thigh, right and left forearms) of six exposure metrics. Less common positive associations with captan exposure were found for increasing applicator age (left thigh) and using a tank mix additive (left forearm); a negative

association was found for washing hands after mixing (left forearm).

Exposure determinants—models with application method

In the set of models more analogous to the AHS algorithm, application method was an important determinant of air and hand exposures (Table 5). Air-blast application was associated with an ~4- to 5-fold

Table 5. Multiple linear regression models for captan in air, hand rinse, thigh patch, and forearm patch samples: application method included as the measure of application size

Dependent variable	<i>n</i>	β	SE	<i>P</i> -value	Factor ^a
Air: ln(captan, $\mu\text{g m}^{-3}$)					
Intercept	136	-0.6115	0.7034	0.39	
Application method (AB/HS = ref.)		1.4895	0.2986	<0.0001	4.4
Captan formulation (WP/liquid = ref.)		3.0759	0.6537	<0.0001	22
Hand: ln(captan, μg)					
Intercept	138	5.1238	0.4129	<0.0001	
Wore CR gloves—mixing (Y/N = ref.)		-1.6644	0.3680	<0.0001	0.19
Application method (AB/HS = ref.)		1.5531	0.4175	0.0004	4.7
Mean concentration captan in tank (mg l^{-1})		0.2901	0.1250	0.023	1.3
R. thigh: ln(captan, μg)					
Intercept	136	1.5827	1.1554	0.18	
Additive used (Y/N = ref.)		1.9662	0.5942	0.0015	7.1
Wore CR gloves—applying (Y/N = ref.)		-1.5796	0.4864	0.0018	0.21
Wore coverall/suit—mixing (Y/N = ref.)		-0.9659	0.4019	0.019	0.38
Captan formulation (WP/liquid = ref.)		2.7018	1.1658	0.023	14.9
L. thigh: ln(captan, μg)					
Intercept	134	1.3937	1.1165	0.22	
Wore coverall/suit—mixing (Y/N = ref.)		-2.0721	0.5327	0.0002	0.13
Captan formulation (WP/liquid = ref.)		3.0259	1.1308	0.0093	21
R. forearm: ln(captan, μg)					
Intercept	137	1.9080	0.7022	0.0083	
Additive used (Y/N = ref.)		1.2987	0.4539	0.0055	3.7
Captan formulation (WP/liquid = ref.)		1.9489	0.6993	0.0068	7.0
Wore coverall/suit – mixing (Y/N = ref.)		-1.0823	0.4265	0.013	0.34
L. forearm: ln(captan, μg)					
Intercept	138	2.1543	0.5778	0.0004	
Additive used (Y/N = ref.)		2.1322	0.5242	0.0001	8.4
Tree fruit stage (Late/early = ref.)		1.5291	0.4615	0.0015	4.6
Wore CR gloves – mixing (Y/N = ref.)		-1.6647	0.5115	0.0017	0.19
Repaired spray equipment (Y/N = ref.)		1.1074	0.3834	0.0051	3.0

R, right; L, left; ref., referent; WP, wettable powder.

^aexp(β). Dichotomous variable: multiplicative factor by which captan exposure increases or decreases from reference condition. Continuous variable: multiplicative factor by which captan exposure increases (or decreases) when variable (e.g. application method) increases (or decreases) by a multiplicative factor of e (i.e. 4.4).

higher hand and air captan exposures than hand spray application. As in models that included kilogram captan a.i applied, formulation was a determinant of air, right and left thigh, and right forearm exposure but not of hand or left forearm exposure. Wearing CR gloves during mixing significantly reduced captan exposure to the hands and left forearm (81% each); wearing CR gloves while applying significantly reduced exposure to the right thigh (79%). Wearing a coverall/suit while mixing significantly reduced exposure to the right and left thighs (62 and 87%, respectively) and to the right forearm (66%). Wearing

both a coverall/suit during mixing and CR gloves while applying reduced right thigh exposure by a combined 92%. A one unit (milligrams per liter) increase in the mean concentration of captan in the tank was associated with an ~30% increase in captan exposure to the hand. Including an additive in the tank mix was also associated with increased captan exposure to the right and left forearms (4- and 8-fold, respectively) and to the right thigh (7-fold). Spraying after petal fall (late, when foliage is denser) and repairing spray equipment were significantly and positively associated with exposure for only the left forearm.

Modification of the algorithm

The first three variables in the AHS algorithm, mixing status [MIX], application method [APPLY], and equipment repair [REPAIR] are summed and then multiplied by a [PPE] reduction factor to give an exposure intensity score (Dosemeci *et al.*, 2002). [MIX], [APPLY], and [REPAIR] are assigned weights that reflect the extent to which the variable condition contributes to exposure, i.e. higher weights indicate greater exposure intensity. The [PPE] reduction factor (0.1 = maximum protection and 1 = no protection) reflects the amount of PPE worn by the applicator.

In the original AHS algorithm, airblast and hand spray application methods were given equal weights of 9 for [APPLY]. Based on our finding that airblast was associated with a 4- to 5-fold increase in air and hand exposure as compared to hand spray, we revised the airblast and hand spray [APPLY] weights to 9 and 2, respectively. We also found the reduction in exposure to the hand, right thigh, and left forearm from wearing CR gloves averaged ~80% (PPE reduction factor of 0.2) and the reduction in exposure to the right and left thighs and right forearm from wearing a coverall/suit averaged ~70% (PPE reduction factor of 0.3) (Table 5), with a combined PPE reduction factor for both CR gloves and coverall/suit of ~0.1. This is in contrast to the AHS algorithm where wearing CR gloves decreased exposure by 40% (reduction factor of 0.6), wearing a coverall/suit by 30% (reduction factor of 0.7). Thus, the PPE reduction factors in our adjusted algorithm were 1.0 (no PPE), 0.3 (coverall/suit only worn), 0.2 (CR gloves only worn), and 0.1 (both CR gloves and coverall/suit worn). The [REPAIR] and [MIX] variables were left unchanged. These algorithm adjustments were made solely on the results of the air, hand, and patch analyses and then used in a correlation analysis with urinary THPI. Correlation of algorithm scores with urinary THPI improved substantially for all THPI measures using the adjusted algorithm as compared to the original algorithm (Table 7). Statistical significance was reached for the concentration of THPI in the first-morning sample on Day 1 ($P = 0.04$) and results approached significance for the 24-h THPI concentration ($P = 0.08$).

Variance components

Including kilogram captan a.i. in the models generally improved the percentage of the total variance explained by the fixed effects as compared to models with application method, except for the hands where the percent fixed was similar under both model conditions (Table 6). For models including kilogram captan a.i., the percentage of the total variance explained

by the fixed effects ranged from 37.5 to 48.4%; for models including application method, the percent fixed ranged from 26 to 44%. In the worker-only models, the proportion of the total variance in the between-worker component was substantially higher than in the within-worker component for all exposure metrics.

DISCUSSION

We have developed models that identify important determinants of captan exposure among orchard applicators in the AHS. The first set of models (Table 4), which include kilogram of captan a.i. as a measure of application size, are the strongest predictive models; the second set of models (Table 5), which include application method as a measure of application size, are most comparable to the AHS pesticide exposure intensity algorithm. In addition to kilogram captan a.i. and airblast application, determinants of increased captan exposure in one or more models included formulation, repairing spray equipment, use of a spray additive, applicator age, and late tree fruit stage. Determinants associated with decreased exposure in one or more models included wearing CR gloves during mixing and applying, wearing a coverall/spray suit while mixing, and washing hands after mixing. Although use of an enclosed cab while spraying captan was identified as an exposure determinant in Dutch orchards (de Cock *et al.*, 1998), we did not find this effect in either univariate or multiple regression analyses, possibly because an enclosed cab was present on only 12% of the monitored days.

Formulation was an important exposure determinant for air, thigh, and forearm exposures (Table 5). On 98% of the days that captan was detected in air samples, applicators handled a wettable powder formulation while mixing. Among patch samples with detectable captan levels, the percentage of samples where applicators used a wettable powder was also high [right thigh (94%), left thigh (95%), right forearm (93%), and left forearm (93%)]. Wettable powder formulations are more likely to become airborne during mixing than liquid formulations and therefore more available for inhalation or deposition on the body. Exposure differences related to product formulation have been previously reported for pesticide urinary biomarkers (Arbuckle *et al.*, 2002; Alexander *et al.*, 2006; Thomas *et al.*, 2010b). Formulation was not a determinant of hand exposure, possibly because the hands were equally likely to contact liquid and wettable powder formulations

Table 6. Variance components for air, hand rinse, and patch samples reported separately for multiple regression models that included as a measure of application size either kilogram captan a.i. applied or application method. Total variance was computed from a model containing worker-only as a random effect

Application size measure		Worker-only model			Model with random and fixed effects				
		Total (between and within)	Variance ratio ^a , between-worker	Variance ratio ^a , within-worker	Between-worker		Within-worker		Fixed ^b
					$\tau S^2_y(B S^2_y, W S^2_y)$	$B R_{0.95}^c$	$W R_{0.95}^d$	$B S^2_y(\%)$	
Air	k.g. captan a.i.	2.52 (1.87, 0.65)	212	24	0.51 (20.2)	2.0	0.79 (31.4)	2.4	48.4
	application method	2.52 (1.87, 0.65)	212	24	0.70 (27.8)	2.3	0.71 (28.2)	2.3	44.0
Hand	k.g. captan a.i.	4.87 (3.81, 1.06)	2100	57	1.83 (37.6)	3.9	1.05 (21.6)	2.8	40.8
	application method	4.87 (3.81, 1.06)	2100	57	1.77 (36.3)	3.8	1.06 (21.8)	2.8	41.9
R. thigh	k.g. captan a.i.	8.86 (8.02, 0.84)	66300	36	4.82 (54.4)	9.0	0.52 (5.8)	2.1	39.8
	application method	8.86 (8.02, 0.84)	66300	36	5.54 (62.5)	10.5	0.60 (6.8)	2.2	30.7
L. thigh	k.g. captan a.i.	9.12 (7.66, 1.46)	51500	114	3.67 (40.2)	6.8	1.26 (13.8)	3.1	46.0
	application method	9.12 (7.66, 1.46)	51500	114	5.41 (59.3)	10.2	1.34 (14.7)	3.2	26.0
R. forearm	k.g. captan a.i.	5.62 (3.70, 1.92)	1880	229	2.10 (37.4)	4.3	1.38 (24.6)	3.2	38.0
	application method	5.62 (3.70, 1.92)	1880	229	2.11 (37.5)	4.3	1.90 (33.8)	4.0	28.7
L. forearm	k.g. captan a.i.	6.21 (4.55, 1.66)	4300	156	3.27 (52.6)	6.1	0.62 (9.9)	2.2	37.5
	application method	6.21 (4.55, 1.66)	4300	156	3.20 (51.5)	6.0	0.88 (14.2)	2.6	34.3

K (number of individuals) = 72; N (number of measurements) = 134 (l. thigh), 136 (air, r. thigh), 137 (r. forearm), and 138 (hand and l. forearm). τS^2_y , total variance; $B S^2_y$, between-worker variance; $B GSD$, between-worker GSD; $W S^2_y$, within-worker variance; $W GSD$, within-worker GSD; R, right; L, left; LOD, limit of detection.

^aCaution should be used when comparing variance ratios computed using maximum likelihood estimation methods for data below the LOD (as we did) to variance ratios computed using substitution methods (e.g. LOD/2) for data below the LOD.

^bPercentage of the total variance explained by the fixed effects, i.e. % fixed = $100 - [B S^2_y(\%) + W S^2_y(\%)]$ in model with random (worker) and fixed effects.

^cComputed as: $e^{[3.92 \ln(B GSD)]}$.

^dComputed as: $e^{[3.92 \ln(W GSD)]}$.

during mixing. Whether formulation affects dermal uptake is unclear.

The above determinants were derived from models that used external metrics (air, hand, and dermal patches) as exposure measures; however, we also measured urinary THPI as a biomarker of captan exposure. If the external metrics we measured included the important routes of exposure, then exposure determinants identified for these external metrics should similarly modify THPI levels in the urine. To test this notion, we adjusted the algorithm to be consistent with our model results by changing the relative weights for airblast and hand spray in the [APPLY] variable and changing the [PPE] variable weights for wearing CR gloves and/or a coverall/suit. The correlation of the adjusted algorithm with urinary THPI improved substantially, going from highly non-significant using the original algorithm to statistically significant or nearly statistically significant for several THPI measures (Table 7). This improved correlation suggests that changes to the AHS algorithm to increase the contrast between airblast and hands pray and to increase the PPE reduction factor for wearing CR gloves and a coverall/suit should improve pesticide exposure intensity estimates for orchard applicators.

Some caveats should be noted in applying determinants identified from external measures to urinary THPI. First, dermal and urine sampling were conducted concurrently and the dermal sampling techniques we used, removal (hands) and interception (patches), could underestimate THPI levels by interfering with uptake. Second, THPI is a low abundance captan metabolite (1–2%; Krieger and Thongsinthusak, 1993), which could limit detection of THPI at low

exposures. Third, the effect of wearing a respirator could not be evaluated because the external exposure metrics were unaffected by respirator use.

Studies of workers applying pesticides to either crops, turf, or animals have reported reductions in pesticide exposure due to glove use of 82% (de Cock *et al.*, 1998), 96% (Stewart *et al.*, 1999), 71–98% (Hines *et al.*, 2001), 78% (Harris *et al.*, 2002), 62% (2,4-dichlorophenoxyacetic acid but no effect on 4-chloro-2-methylphenoxyacetic acid (Arbuckle *et al.*, 2002), 85% (Acquavella *et al.*, 2004), 27% (Alexander *et al.*, 2006), 81% (Alexander *et al.*, 2007), and 77–94% (Thomas *et al.*, 2010b). These exposure reduction estimates were obtained by either comparing reported GMs for glove versus no glove use or exponentiating the regression coefficient from models where glove use was a dichotomous (yes/no) independent variable and the dependent exposure variable had been log-transformed. While the exposure metric and pesticide varied across studies, these studies as well as our study suggest reductions in pesticide exposure intensity due to glove use range from ~60 to >95%. The association we observed between use of CR gloves and reduced exposure to the thighs was also observed for three herbicides in a study of custom applicators (Hines *et al.*, 2001).

We found higher between-worker variance as compared to within-worker variance ratios for our pesticide applicators (Table 6), indicating that observed differences in exposures were largely driven by individual behaviors and work practices. This contrasts with other studies of pesticide and non-pesticide agricultural exposures where variance ratios were higher for the within- as compared to the between-worker distributions (Kromhout and Heederik,

Table 7. Correlation of urinary THPI measures with the original AHS pesticide exposure intensity algorithm and with the adjusted algorithm

THPI exposure measure ^a	<i>n</i>	%>LOD	Original algorithm		Adjusted algorithm	
			β^b	<i>P</i> -value	β^b	<i>P</i> -value
24-h conc., $\mu\text{g l}^{-1}$	130	NA ^c	0.0001	1.0	0.0307	0.08
24-h mass, μg	130	NA ^c	-0.0035	0.84	0.0284	0.14
Mass, first-morning, Day 1, μg	140	61.4	-0.011	0.63	0.0411	0.12
Conc., first-morning, Day 1, $\mu\text{g g}^{-1}$ creatinine	140	61.4	0.0016	0.94	0.0498	0.04
Excretion rate, overnight (Day 0 to Day 1), $\mu\text{g h}^{-1}$	117	59.8	-0.015	0.56	0.0367	0.15

Conc., concentration; LOD, limit of detection; NA, not applicable.

^aUrinary THPI levels previously reported in Hines *et al.* (2008).

^bThe estimated regression coefficient and *P*-value were computed using MLE via PROC NL MIXED 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 measurements 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 the PROC MIXED procedure with person treated as a random effect.

^cThe percentage of days where all samples comprising the summed 24-h total had THPI levels below the LOD was 24% for airblast and 55% for hand spray.

2005). Our study participants were private farmers with fixed orchard acreage who sprayed captan on both days. From day-to-day, they tended to use the same equipment and PPE while spraying and to spray similar total acreage, conditions that would likely reduce day-to-day variability. For example, on the two sampled days, >90% of the applicators matched on formulation type, application method, glove use, and coverall/spray suit use. We also found a difference of $\leq 15\%$ in $\ln(\text{kilogram of captan sprayed})$, $\ln(\text{number of acres sprayed})$, and $\ln(\text{duration of application})$ for 54, 67, and 94% of the applicators, respectively, between the two sampled days. This day-to-day consistency in application size-related covariates is in contrast to agricultural commercial applicators whose day-to-day spraying activities depend on customer needs and who have higher day-to-day than between-worker variability (Hines *et al.*, 2001). Differences in the relative magnitude of the within- and between-worker variance ratios in agriculture (or any other work environment) are likely related to the particular characteristics of the tasks performed, the control measures used, and environmental conditions.

The higher total variability we observed for dermal as compared to air exposures is consistent with that reported in other studies (Kromhout *et al.*, 1993). In all our models, >50% of the total variability was not explained by the fixed effects. Partitioning this unexplained variability into within- and between-worker components is useful for understanding the degree to which factors that influence exposures between workers (e.g. work practices, equipment differences, PPE use) and factors that influence day-to-day exposures within workers (e.g. workload, amount of chemical used, changes in PPE use, meteorological conditions) underlie the unexplained variability. For example, for body and hand exposures, generally more of the unexplained variability was between workers as compared to within workers; however, the reverse was true for air exposures, suggesting a different focus is needed for identifying additional exposure determinants for dermal and air exposures.

Our results highlight several important issues for pesticide exposure assessment. First, pesticide exposure determinants can be body site and exposure route specific, e.g. formulation was an important determinant of captan air, thigh, and forearm exposure, but not of hand exposure, a difference having implications for understanding exposure mechanisms and for methods to reduce exposure. This dependency of pesticide exposure determinants on site/route sampled has been previously reported in Dutch orchards

(de Cock *et al.*, 1998) and in AHS applicators applying 2,4-D (Thomas *et al.*, 2010b). Second, given the importance that formulation can play in pesticide exposures together with the difficulty applicators can have recalling-specific formulations for products used in the past, including difficulty distinguishing between formulation of the purchased product and the physical state of the applied material, better methods are needed to capture product formulation in epidemiological studies. Third, application method appears to be a useful surrogate for measures of application size in specific situations; a not unreasonable notion in that methods used to apply pesticides to small acreages may not be practical for large acreages.

Finally, we note that the range of reduction afforded by the use of CR gloves reported in the literature is quite wide (27–98%). It is unclear if differences in glove composition, glove age, manner of wearing gloves, product formulation, or other factors explain this variability. In an exploratory analysis using a one-way analysis of variance (NLMIXED) with three levels of glove age (no/old/new glove) with worker as a random effect, we found that glove age was significant for hand exposure only when worn during application ($P = 0.018$) but not mixing, marginally significant if adjusted for kilogram of captan applied ($P = 0.051$), and not significant in a full multiple regression model (data not shown). Thus, future studies should examine glove performance factors in detail.

Strengths of this study include a large sample size, detailed observations of applicator activities, and repeated measurements to allow estimation of within- and between-worker distributions. We had only two repeat measurements per applicator, a number that was constrained by the frequency of seasonal captan applications across the group. Kromhout *et al.* (1993) found that both the number of measurements and the number of workers had a negligible effect on the between-worker variance ratio, but a significantly greater influence on the within-worker variance ratio when the total number of measurements was >25 and the total number of workers >7, conditions that were met in our study. It is possible that if the observational period had been longer and additional measurements collected on each worker, we might have observed larger within-worker variance ratios.

Study limitations include a significant amount of left-censoring in our exposure metrics (44–54%); however, bias in parameter estimates due to left-censoring was minimized by using MLE techniques. Caution should be used in interpreting the magnitude of the regression coefficients for formulation in our models due to the small number (≤ 5) of air and

patch samples with detectable values among applicators using a liquid formulation. Univariate analyses included a large number of comparisons and some statistically significant findings could have occurred by chance. If interested, the reader could perform a Bonferroni multiple comparison correction on a selected set of covariates. Because this was an observational study with applicators choosing their work practices and equipment, we could not randomize potential exposure determinants. The AHS participants in this study were all private farmer applicators and exposure determinants identified for this group may not be entirely applicable to commercial applicators or to other a.i.s.

In summary, the most consistent determinants of captan exposure among the AHS orchard applicators were a measure of application size (either kilogram captan a.i. applied or application method), wearing CR gloves and/or a coverall/suit, repairing spray equipment, and product formulation. Adjustment of the [APPLY] and [PPE] variable weights in AHS pesticide exposure algorithm based on our findings substantially improved the correlation between the AHS algorithm and urinary THPI levels. Since the unexplained variability was largely in the between-worker component, future efforts to identify additional determinants of AHS orchard applicator pesticide exposures should focus on behavioral and work practice factors that vary between applicators rather than factors that vary from day-to-day.

FUNDING

This work has been supported in part by the Intramural research program of the National Institute for Occupational Safety and Health; National Institutes of Health, National Cancer Institute (Z01-CP010119); National Institute of Environmental Health Sciences (Z01-ES049030).

Acknowledgements—We gratefully acknowledge the contribution of the AHS participants to this study. We would like to thank Dr Yan Jin at NIOSH for statistical contributions.

Disclaimer—The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health. Mention of any company or product does not constitute endorsement by the National Institute for Occupational Safety and Health.

REFERENCES

- Acquavella JF, Alexander BH, Mandel JS *et al.* (2006) Exposure misclassification in studies of agricultural pesticides: insights from biomonitoring. *Epidemiology*; 17: 69–74.
- Acquavella JF, Alexander BH, Mandel JS *et al.* (2004) Glyphosate biomonitoring for farmers and their families: results from the Farm Family Exposure Study. *Environ Health Perspect*; 112: 321–6.
- Alavanja MCR, Sandler DP, McDonnell CJ *et al.* (1999) Characteristics of persons who self-reported a high pesticide exposure event in the Agricultural Health Study. *Environ Res*; 80: 180–6.
- Alavanja MCR, Sandler DP, McMaster SB *et al.* (1996) The agricultural health study. *Environ Health Perspect*; 104: 362–9.
- Alexander VH, Burns CJ, Bartels MJ *et al.* (2006) Chlorpyrifos exposure in farm families: results from the farm family exposure study. *J Expo Sci Environ Epidemiol*; 16: 447–56.
- Alexander BH, Mandel JS, Burns CJ *et al.* (2007) Biomonitoring of 2,4-dichlorophenoxyacetic acid exposure and dose in farm families. *Environ Health Perspect*; 115: 370–6.
- Arbuckle TE, Burnett R, Cole D *et al.* (2002) Predictors of herbicide exposure in farm applicators. *Int Arch Occup Environ Health*; 75: 406–14.
- Bakke B, De Roos AJ, Barr DB *et al.* (2009) Exposure to atrazine and selected non-persistent pesticides among corn farmers during a growing season. *J Expo Sci Environ Epidemiol*; 19: 544–54.
- Baldi I, Lebaillly P, Jean S *et al.* (2006) Pesticide contamination of workers in vineyards in France. *J Expo Sci Environ Epidemiol*; 16: 115–24.
- Coble J, Arbuckle T, Lee W *et al.* (2005) The validation of a pesticide exposure algorithm using biological monitoring results. *J Occup Environ Hyg*; 2: 194–201.
- de Cock J, Heederick D, Kromhout H *et al.* (1998) Determinants of exposure to captan in fruit growing. *Am Ind Hyg Assoc J*; 59: 166–72.
- Dosemeci M, Alavanja MCR, Rowland AS *et al.* (2002) A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. *Ann Occup Hyg*; 46: 245–60.
- Geer LA, Cardello N, Dellarco MJ *et al.* (2004) Comparative analysis of passive dosimetry and biomonitoring for assessing chlorpyrifos exposure in pesticide workers. *Ann Occup Hyg*; 48: 683–95.
- Harris SA, Sass-Kortsak AM, Corey PN *et al.* (2002) Development of models to predict dose of pesticides in professional turf applicators. *J Expo Anal Environ Epidemiol*; 12: 130–44.
- Hines CJ, Deddens JA, Jaycox LB *et al.* (2008) Captan exposure and evaluation of a pesticide exposure algorithm among orchard pesticide applicators in the Agricultural Health Study. *Ann Occup Hyg*; 52: 153–66.
- Hines CJ, Deddens JA, Coble J *et al.* (2007) Fungicide application practices and personal protective equipment use among orchard farmers in the Agricultural Health Study. *J Agric Safety Health*; 13: 205–23.
- Hines CJ, Deddens JA, Tucker SP *et al.* (2001) Distributions and determinants of pre-emergent herbicide exposures among custom applicators. *Ann Occup Hyg*; 45: 227–39.
- Jin Y, Hein MJ, Deddens JA *et al.* (2011) Lognormally distributed exposure data with repeated measures and values below the limit of detection using SAS. *Ann Occup Hyg*; 55: 97–112.
- Krieger RI, Thongsinthusak T. (1993) Captan metabolism in humans yields two biomarkers, tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA) in urine. *Drug Chem Toxicol*; 16: 207–25.

- Kromhout H, Heederik K. (2005) Effects of errors in the measurement of agricultural exposures. *Scand J Work Environ Health*; 31: 33–8.
- Kromhout H, Symanski E, Rappaport SM. (1993) A comprehensive evaluation of within- and between-worker components of occupational exposure to chemical agents. *Ann Occup Hyg*; 37: 253–70.
- Lebailly P, Bouchart V, Baldi I *et al.* (2009) Exposure to pesticides in open-field farming in France. *Ann Occup Hyg*; 53: 69–81.
- NIOSH (2003) Manual of analytical methods (NMAM). NIOSH Schlect PC and O'Connor PF, editors. (Suppl. 3) 4th edn. Cincinnati, OH: Department of Health and Human Services, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health DHHS (NIOSH) Pub. No. 2003-154.
- Stewart PA, Fears T, Kross B *et al.* (1999) Exposure of farmers to phosmet, a swine insecticide. *Scand J Work Environ Health*; 25: 33–8.
- Thiébaud R, Guedj J, Jacqmin-Gadda H *et al.* (2006) Estimation of dynamical model parameters taking into account undetectable marker values. *BMC Med Res Methodol*; 6: 38.
- Thomas K, Dosemeci M, Coble J *et al.* (2010a) Assessment of a pesticide exposure intensity algorithm in the Agricultural Health Study. *J Expos Sci Environ Epidemiol*; 20: 559–69.
- Thomas K, Dosemeci M, Hoppin JA *et al.* (2010b) Urinary biomarker, dermal, and air measurement results for 2,4-D and chlorpyrifos farm applicators in the Agricultural Health Study. *J Expos Sci Environ Epidemiol*; 20: 119–134.