Journal of Exposure Science and Environmental Epidemiology (2012) 22, 584–592

www.nature.com/jes

ORIGINAL ARTICLE

# Lifetime organophosphorous insecticide use among private pesticide applicators in the Agricultural Health Study

Jane A. Hoppin[1], Stuart Long[2], David M. Umbach[3], Jay H. Lubin[4], Sarah E. Starks[5], Fred Gerr[5], Kent Thomas[6], Cynthia J. Hines[7], Scott Weichenthal[8], Freya Kamel[1], Stella Koutros[9], Michael Alavanja[9], Laura E. Beane Freeman[9] and Dale P. Sandler[1]

Organophosphorous insecticides (OPs) are the most commonly used insecticides in US agriculture, but little information is available regarding specific OP use by individual farmers. We describe OP use for licensed private pesticide applicators from Iowa and North Carolina in the Agricultural Health Study (AHS) using lifetime pesticide use data from 701 randomly selected male participants collected at three time periods. Of 27 OPs studied, 20 were used by $>1\%$. Overall, 95% had ever applied at least one OP. The median number of different OPs used was 4 (maximum = 13). Malathion was the most commonly used OP (74%) followed by chlorpyrifos (54%). OP use declined over time. At the first interview (1993–1997), 68% of participants had applied OPs in the past year; by the last interview (2005–2007), only 42% had. Similarly, median annual application days of OPs declined from 13.5 to 6 days. Although OP use was common, the specific OPs used varied by state, time period, and individual. Much of the variability in OP use was associated with the choice of OP, rather than the frequency or duration of application. Information on farmers' OP use enhances our ability to characterize and understand the potential health effects of multiple OP exposures.

*Journal of Exposure Science and Environmental Epidemiology* (2012) **22,** 584–592; doi:10.1038/jes.2012.79; published online 1 August 2012

**Keywords:** pesticide use; farming; organophosphorous insecticide

## INTRODUCTION

In 2007, 93 million pounds of insecticides were used in the United States with 70% used in agriculture.[1] Over a third of these were organophosphorous insecticides (OPs), a class of insecticides introduced in the 1950s. Although their use has declined over time, OPs are still among the most commonly used insecticides in the United States.[1] Although national and regional data are available on pesticide application and sales,[1–3] only limited information is available regarding use of specific pesticides by individuals, particularly how many pesticides of a given class an individual uses in a year or lifetime. Information on pesticide use patterns in the United States is limited to national surveys of pesticide applicators, state-specific data about use on specific commodity crops, and sales figures.[1–3] These surveys provide information about the relative ranking of specific pesticides used in the United States, either by pounds of active ingredients applied or dollars spent on specific pesticides.[1] For commodity crops, information is also available regarding the pesticides used on each crop by state and calendar year.[2,3] Since 1990, CA has collected information on agricultural use of pesticides, including the amount of active ingredient and the location where the pesticide was applied.[4] All these sources are helpful in identifying the key pesticides used, but none provides information regarding the frequency of use for an individual applying these pesticides. Of particular interest for health research is understanding how pesticides in a given class are used by individuals.

OPs represent a large class of insecticides. They are often evaluated together based on their ability to inhibit acetylcholinesterase (AChE).[5] This mechanism may not be related to all health outcomes,[6–8] nor do all OPs have the same capacity to inhibit AChE.[9] The biomarkers most frequently used to assess exposure to OPs (e.g., dialkylphosphates or AChE inhibition) are non-specific and thus have limited ability to assign exposure to a specific chemical.[10] As OPs differ in their toxicities and potential to affect human health, it is critical to understand how use of specific OPs differs among individuals. To characterize OP usage by US farmers, we used data from a random sample of private pesticide applicators in the Agricultural Health Study (AHS), a prospective cohort study of licensed pesticide applicators in Iowa (IA) and North Carolina (NC).[11] Using data collected at three time points during 1993–2007, we describe among a well-characterized group of farmers: (1) the frequency of use of specific OPs, (2) the number of different OPs used, (3) the number of days spent applying OPs, and (4) temporal changes in use by this group.

## METHODS

### Population

Pesticide applicators enrolled between 1993–1997 (Phase 1) when they were receiving or renewing their pesticide licenses.[11] A total of 82% of eligible private applicators (mainly farmers) enrolled. In Phase 1, all pesticide applicators completed the AHS enrollment questionnaire and ~44% also

[1]Epidemiology Branch, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; [2]Westat, Durham, North Carolina, USA; [3]Biostatistics Branch, NIEHS, NIH, DHHS, Research Triangle Park, North Carolina, USA; [4]Biostatistics Branch, NCI, NIH, DHHS, Rockville, Maryland, USA; [5]College of Public Health, University of IA, Iowa City, Iowa, USA; [6]EPA, Human Exposure and Atmosphere Science Division, Research Triangle Park, North Carolina, USA; [7]Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, Ohio, USA; [8]Health Canada, Ottawa, Ontario, Canada and [9]OEEB, DCEG, NCI, Rockville, Maryland, USA. Correspondence: Dr. Jane A. Hoppin, Epidemiology Branch, NIEHS, NIH, DHHS, MD A3-05, PO Box 12233, Research Triangle Park, NC 27709-2233, USA.
Tel.: +1919 541 7622. Fax: +1919 541 2511.
E-mail: hoppin1@niehs.nih.gov
Received 17 February 2012; accepted 16 May 2012; published online 1 August 2012

completed the take-home questionnaire.[11] Approximately 5 and 10 years after enrollment (Phase 2: 1999–2003; Phase 3: 2005–2010), all AHS participants were asked to complete telephone interviews to update their pesticide use history. This analysis focuses on a subset of applicators who completed their Phase 3 interview by 2007.

We assessed lifetime use of OPs among 701 AHS private pesticide applicators recruited for participation in a neurological testing study.[12] The OP exposure histories of these individuals were enhanced to include data not currently available in the main AHS data set, specifically frequency and duration of use for pesticides on the take-home checklist and resolution of unknown insecticides from the follow-up interviews (see below for more information on exposure assessment). Private pesticide applicators who completed all questionnaires at all three phases were eligible. Participants were selected based on their lifetime days of use of 10 OPs at Phase 1.[12] This selection variable was the sum of the lifetime days of use of each of the 10 OPs for which detailed information was collected at enrollment. As the neurological study required traveling to a fixed site for testing, only applicators living within 150 miles of Iowa City, IA; Dubuque, IA; Greenville, NC; or Wilmington, NC, were eligible.[12] Women were excluded from the sample because of their low representation (<3%) among the AHS applicators. We created two strata within each state — a high exposure group and the remainder of the population — based on lifetime OP days of use, and we oversampled those in the high-exposure stratum in each state. In IA, the high-exposure stratum included the top 20% of the distribution of lifetime days; in NC, the high-exposure stratum included the top 34%. In NC, we selected a larger fraction because the number of NC participants is smaller and they are more geographically dispersed. We randomly sampled equal numbers from all eligible individuals in each of the four state-by-exposure strata and identified empirical sampling weights (i.e., number of subjects participating/number of subjects eligible) to estimate pesticide use histories for the AHS participants ($N = 3863$) who met the eligibility requirements for the neurological study. The overall response rate was ~39%.

## Pesticide Use History

Information on pesticide use was collected in the AHS during three time periods: Phase 1 (1993–1997), Phase 2 (1999–2003), and Phase 3 (2005–2007 for this subset). Individuals were asked about their personal application of pesticides for crop, animal, and non-crop uses. Phase 1 consisted of two self-administered questionnaires, the enrollment and the take-home questionnaire. Both Phase 1 questionnaires collected information regarding frequency and duration of use of selected pesticides in a closed format, such that all individuals provided responses on pre-determined OPs. At Phase 1, participants provided detailed information on 10 specific OPs (Table 1) including ever use, days used per year, years used, and use in the past year. The take-home questionnaire also included a checklist that collected ever-use information on 12 additional OPs. The pesticide-related questions on the Phases 2 and 3 telephone interviews had an open-ended format and obtained information on recent use of pesticides including

**Table 1.** OP information collected in the Agricultural Health Study (1993–2007) and OP subgroup classification.

| *Chemical name* | *Year introduced to market* | *Data collection periods* | | | | *OP subgroup*[b] | *Organothiophosphate group*[b] |
|---|---|---|---|---|---|---|---|
| | | *Phase 1 (1993–1997)*[a] | | *Phase 2 (1999–2003)* | *Phase 3 (2005–2007)* | | |
| | | *Detailed information* | *Take-home checklist* | | | | |
| Acephate | 1973 | | X | X | X | Phosphoramidothioate | |
| Azinphos-methyl | 1959 | | X | X | X | Organothiophosphate | Heterocyclic |
| Chlorethoxyfos | 1995 | | | X | | Organothiophosphate | Aliphatic |
| Chlorpyrifos | 1965 | X | | X | X | Organothiophosphate | Heterocyclic |
| Coumaphos | 1958 | X | | X | X | Organothiophosphate | Heterocyclic |
| Diazinon | 1948 | X | | X | X | Organothiophosphate | Heterocyclic |
| Dichlorvos | 1948 | X | | X | X | Organophosphate | |
| Dicrotophos | 1964 | | | | X | Organophosphate | |
| Dimethoate | 1962 | | X | X | X | Organothiophosphate | Aliphatic |
| Dioxathion | 1952 | | X | | | Organothiophosphate | Heterocyclic |
| Disulfoton | 1961 | | X | X | X | Organothiophosphate | Aliphatic |
| Ethoprop | 1967 | | X | | | Organothiophosphate | Aliphatic |
| Fenamiphos | 1972 | | | X | X | Phosphoramidate | |
| Fenthion | 1965 | | X | | | Organothiophosphate | Phenyl |
| Fonofos | 1967 | X | | X | X | Phosphonothioate | |
| Malathion | 1955 | X | | X | X | Organothiophosphate | Aliphatic |
| Methamidophos | 1972 | | X | | | Phosphoramidothioate | |
| Mevinphos | 1957 | | X | | | Organophosphate | |
| Parathion-methyl | 1954 | X | | X | X | Organothiophosphate | Phenyl |
| Phorate | 1959 | X | | X | X | Organothiophosphate | Aliphatic |
| Phosmet | 1966 | | X | X | X | Organothiophosphate | Heterocyclic |
| Pirimiphos-methyl | 1978 | | | X | | Organothiophosphate | Heterocyclic |
| Ronnel (fenchlophos) | 1955 | | X | | | Organothiophosphate | Phenyl |
| Tebupirimfos | 1995 | | | X | X | Organothiophosphate | Heterocyclic |
| Terbufos | 1974 | X | | X | X | Organothiophosphate | Aliphatic |
| Tetrachlorvinphos | 1966 | | X | X | X | Organophosphate | |
| Trichlorfon | 1954 | X | | | | Phosphonate | |

Abbreviation: OP, organophosphorous insecticide.
[a]Two questionnaires were completed as part of Phase 1.
[b]Classifications based on "Compendium of Pesticide Common Names" at the web site: http://www.alanwood.net/pesticides/index.html.
X = collected on this questionnaire.

| Questionnaire | Phase 1 (1993-1997) | | Phase 2 (1999-2003) | Phase 3 (2005-2007) | |
|---|---|---|---|---|---|
| Metric Created | Detailed Questionnaire | Take Home Questionnaire Checklist | | | Total |
| Ever/never use | "Have you ever personally mixed or applied this pesticide?" Yes/No | What other pesticides have you used? (Mark all that apply.) | "What insecticides, fungicides, fumigants, or herbicides (weed killers) were used on SPECIFIC CROP (ANIMAL, NON-CROP) during Reference Year (last year applied pesticides)?" | "Since year of last interview have you personally used herbicides, insecticides, fungicides, fumigants or any other pesticides for crops (animals, non-crops)? What did you use?" | Ever/never use in lifetime |
| *Assumption/comment:* | *10 OPs included on this list* | *OPs marked are assigned ever use* | *Open form and positive only if reported. Resolved UNKNOWN pesticides.* | *Open form, but prompts based on Phase 2 chemicals; Resolved UNKNOWN pesticides* | |
| Annual application days | "In an average year when you personally used this pesticide, how many days did you do it?" Response in categories | Not asked | "In Reference Year, how many days did you personally mix, load, or apply SPECIFIC PESTICIDE to SPECIFIC CROP?" | "During the years that you applied SPECIFIC PESTICIDE, for how many days per year on average did you personally mix, load, handle or apply it?" | No summary variable created |
| *Assumption/comment:* | | *Days/year for Take Home Chemicals = average days/year for other insecticide application* | *Days/year for each OP; minimum of (i) sum of all uses (Crop, animal, non-crop) or (ii) total days/year of any pesticide application.* | | |
| Years of Application | "How many years did you personally mix or apply this pesticide?" Response in categories | Not asked | Derived from Referent Year | Derived from Referent Year | Total years applied |
| *Assumption/comment:* | | *Years = average number of years applied other insecticides* | *Equal application for all years from Phase 1 to referent year* | *Equal application for all years from last interview (Phase 2) to referent year* | |
| Lifetime days of use | Days/year X Years application (median of categories) | Days/year X Years application | Days/year X Years application | Days/year X Years application | Total lifetime days |

Copies of the AHS Questionnaires are available at www.aghealth.org/questionnaires.html.

**Figure 1.** Creation of lifetime days of organophosphorous insecticide (OP) use based on three Agricultural Health Study (AHS) surveys.

specific product used and the number of days of use. The use of an open-ended format allowed reporting of all pesticides used, by either brand name or chemical name, thus permitting identification of all pesticides in a product. We linked this information to the pesticide active ingredients to identify all the OPs used (see online Supplement). AHS questionnaires are available at www.aghealth.org\questionnaires.html.

The goal of this analysis was to characterize use of specific OPs with regard to duration and frequency of use. Figure 1 outlines the data collection strategy for each phase including how information on OPs was collected and how key variables were created. We provide more detailed information on data collection and pesticide variable creation in the online Supplement. For each OP, we created variables for ever use (yes/no) and days of use (days) for each phase. Days of use for each phase was calculated as the product of the frequency of application (days/year) and the duration of application (years in that reporting period for that individual). From these phase-specific variables, we created variables for lifetime ever use (yes/no) and total lifetime days of use (lifetime days), equal to the sum of all days of use in each phase. Results are presented for the 20 specific OPs used by more than 10 participants.

## Creation of OP Subgroups

The class of OPs includes chemicals with differing chemical structures and these differences may influence toxicity. We categorized pesticides classified as OPs (see http://www.alanwood.net/pesticides/index.html)[13] (Table 1) into six mutually exclusive and exhaustive subgroups: organophosphate, organothiophosphate, phosphonate, phosphonothioate, phosphoramidate, and phosphoramidothioate. The organothiophosphates were further categorized into aliphatic, heterocyclic, and phenyl organothiophosphates. For each subgroup, as well as for total OPs, we calculated total lifetime days based on the sum of the lifetime days of all OPs within that subgroup.

## Statistical Analysis

We computed summary statistics for ever use and annual days of use for specific OPs, overall, by state, and by each time period. We used the empirical sample weights to estimate the results back to the source population, namely, the male AHS participants who met the eligibility criteria for the neurological study (completed all AHS interviews and lived within specific geographic regions of IA and NC). We used Spearman's correlation coefficients to assess the correlation between ever use of specific OPs. All analyses were conducted using SAS 9.1.3 and AHS data releases of P1REL071201, P2REL071202, P3REL090500, and REL090500 for the demographic file.

# RESULTS

The 701 participants in this study appeared representative, except for design characteristics, of the source population ($N = 3863$) who

**Table 2.** Characteristics of the study sample of 701 male applicators compared with other larger groups of the AHS cohort.

| | *Current study participants* | *AHS participants who completed all interviews* | | *Completed most recent interview* |
|---|---|---|---|---|
| | | *Eligible regions*[a] | *All regions* | |
| | N = *701* | N = *3863* | N = *9841* | N = *19,299* |
| | % | % | % | % |
| *Age (years) in 2006* | | | | |
| <50 | 12 | 12 | 12 | 14 |
| 50–59 | 29 | 25 | 25 | 27 |
| 60–69 | 29 | 26 | 26 | 26 |
| 70–79 | 22 | 25 | 25 | 22 |
| 80+ | 9 | 12 | 12 | 10 |
| *State* | | | | |
| NC | 49 | 45 | 31 | 37 |
| IA | 51 | 55 | 69 | 63 |
| *Education* | | | | |
| <High school | 51 | 58 | 54 | 55 |
| >High school | 49 | 42 | 46 | 45 |
| *Still farming* | | | | |
| At Phase 2 | 79 | 79 | 83 | 82 |
| At Phase 3 | 69 | 67 | 73 | 72 |
| *Still applying pesticides* | | | | |
| At Phase 2 | 90 | 86 | 88 | 87 |
| At Phase 3 | 78 | 69 | 69 | 68 |
| *Farm size at enrollment (acres)* | | | | |
| <5 | 7 | 6 | 8 | |
| 5–49 | 13 | 12 | 10 | 11 |
| 50–199 | 25 | 26 | 18 | 19 |
| 200–499 | 29 | 31 | 30 | 29 |
| 500–999 | 17 | 16 | 22 | 21 |
| >1000 | 10 | 9 | 12 | 12 |
| *Years applied pesticides at enrollment* | | | | |
| <6 | 10 | 11 | 11 | 12 |
| 6–10 | 12 | 12 | 13 | 14 |
| 11–20 | 30 | 33 | 32 | 33 |
| 21–30 | 28 | 27 | 27 | 26 |
| >30 | 20 | 18 | 17 | 15 |
| *Annual days of pesticide application at enrollment* | | | | |
| <5 | 15 | 18 | 19 | 19 |
| 5–9 | 19 | 25 | 26 | 24 |
| 10–19 | 31 | 30 | 32 | 31 |
| 20–39 | 24 | 18 | 17 | 18 |
| 40–59 | 7 | 5 | 4 | 4 |
| 60+ | 4 | 4 | 3 | 4 |
| *Lifetime days of pesticide application at enrollment* | | | | |
| None | 0 | 0 | 0 | 1 |
| 1–74 | 21 | 24 | 25 | 25 |
| 75–200 | 15 | 20 | 22 | 21 |
| 201–400 | 25 | 26 | 27 | 26 |
| >400 | 38 | 30 | 26 | 27 |
| *Total lifetime days of OPs*[b] | | | | |
| None | 6 | 10 | 12 | 20 |
| ≤80 | 29 | 36 | 44 | 42 |
| >80 | 65 | 54 | 45 | 38 |

Abbreviations: AHS, Agricultural Health Study; IA, Iowa; NC, North Carolina; OP, organophosphorous insecticide.
[a]Eligible regions include those within 150 miles of Dubuque or Iowa City, IA, and Greenville or Wilmington, NC.
[b]OPs included in this estimate are the 10 included on the enrollment questionnaire: chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, and trichlorofon.

had completed all AHS interviews and lived within the geographic regions included in the study (Table 2). Study participants were slightly more likely than non-participants to be still applying pesticides at Phase 3 (78% *vs* 69%), Most other pesticide use and demographic characteristics of the sample were similar to all male participants who completed the Phase 3 interview as well as those who completed all AHS interviews (Table 2). By design, the study included equal number of participants from IA and NC, whereas two-third of the AHS as a whole is from IA. Applicators in the highest quartile of lifetime OP use at Phase 1 were overrepresented by design, consistent with the higher proportion of respondents reporting over 400 days of pesticide application in their lifetime in the sample compared both with their regional cohort (38% *vs* 30%) and to individuals who completed the most recent interview (27%). Although the results have been weighted to reflect the source population, the data as presented in Table 2 appear to be a good representation of all the male applicators who completed the last interview as well ($N = 19{,}299$). Participants in the eligible region represent 36% of those who had completed all AHS interviews, 17% of those who completed the Phase 3 interview (Figure 2a), and 8% of male applicators who enrolled in the AHS (Figure 2b).

Over 95% of the population represented by this sample of AHS participants had ever used OPs. The median number of OPs used in a lifetime was 4 and the maximum was 13 (Table 3). The median for IA farmers was four OPs compared with three for NC. Among the participants, 27 different OPs were reported (Table 1). Of the six subgroups, the majority of the OPs were organothiophosphates ($n = 18$) or organophosphates ($n = 4$). Among the organothiophosphates, seven were aliphatic, eight were heterocyclic, and three were phenyl organothiophosphates. Three additional chemicals are classified as phosphonothioate (fonofos) or phosphoramidothioate (acephate and methamidophos) insecticides. The proportion of applicators who used different subgroups of OPs ranged from 20% for organophosphates to 94% for organothiophosphates. Use of OP subgroups was similar in IA and NC, with the exception of organophosphates that had a smaller proportion of users in NC (6%) compared with IA (32%).

Twenty OPs had been used at least once by more than 10 individuals in our sample (Supplementary Table 1). Malathion was the most commonly used OP, with similar prevalence of use in IA and NC (Figure 3). Chlorpyrifos was the second most commonly used OP in NC. After malathion and chlorpyrifos, the relative ranking of chemicals varied between the states. A number of OPs were used only by NC farmers, most notably acephate, which was reported by 46% of NC participants. Acephate was the third most commonly used OP among NC farmers and seventh overall among the cohort. Tebupirimifos was reported by 18% of IA farmers and no NC farmers. All uses of tebupirimifos were associated with the pesticide product Aztec, which also contains cyfluthrin, a pyrethroid insecticide. For most of the 20 OPs, pairwise correlations for ever use were low (data not shown). Only 17 of the 190 possible pairs had correlation coefficients $>0.2$. The highest correlations were between pairs of OPs used more often in NC, acephate and ethoprop ($r = 0.58$), disulfoton and ethoprop ($r = 0.57$), and acephate and disulfoton ($r = 0.56$).

Although almost all applicators reported applying OPs sometime during their lifetimes, only 68% reported applying OPs in the year before AHS enrollment (Table 4). This estimate includes use of the OPs reported only on the take-home questionnaire checklist (acephate, azinphos-methyl, dimethoate, disulfoton, phosmet, and tetrachlorvinphos). If we excluded the OPs from the take-home checklist where use in the past year was inferred, we estimated that 50% of the cohort applied OPs in the year before enrollment. In Phases 2 and 3, approximately 5 and 10 years after enrollment, 45% and 42% of applicators, respectively, reported applying at least one OP. In Phases 2 and 3, IA applicators were slightly more

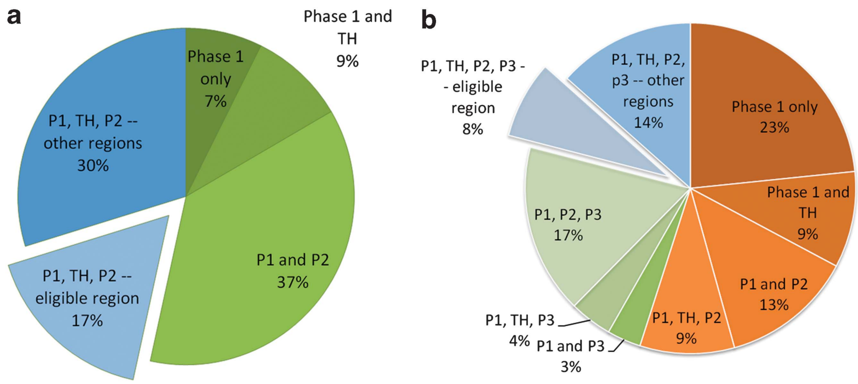


**Figure 2.** Source population for current study in relation to the Agricultural Health Study (AHS) cohort. (a) Source population as fraction of male private applicators who completed Phase 3 interview; (b) Source population as fraction of all male private applicators in the AHS. P1 = Phase 1 enrollment interview. TH = take-home questionnaire at Phase 1. P2 = Phase 2 interview. P3 = Phase 3 interview. Orange shading: did not complete Phase 3 interview. Green shading: completed Phase 3 interview, but not all AHS interviews. Blue shading: completed all AHS interviews.

**Table 3.** Number of organophosphorous insecticides used in a lifetime by participants in the AHS (1993–2007).

| *Chemical group* | *N in chemical group* | *All AHS participants* | | | | *All IA AHS participants* | | | | *All NC AHS participants* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *% Use* | *Median* | *Min* | *Max* | *% Use* | *Median* | *Min* | *Max* | *% Use* | *Median* | *Minimum* | *Maximum* |
| Any organophosphorous | 27 | 95 | 4 | 0 | 13 | 96 | 4 | 0 | 13 | 94 | 3 | 0 | 11 |
| Organophosphate[a] | 4 | 20 | 1 | 1 | 2 | 32 | 1 | 1 | 2 | 6 | 1 | 1 | 2 |
| *Organothiophosphate*[a] | 18 | 94 | 3 | 1 | 11 | 95 | 3 | 1 | 11 | 93 | 3 | 1 | 10 |
| Aliphatic[a] | 7 | 89 | 2 | 1 | 6 | 90 | 2 | 1 | 6 | 87 | 2 | 1 | 6 |
| Heterocyclic[a] | 8 | 75 | 1 | 1 | 5 | 80 | 1 | 1 | 5 | 70 | 1 | 1 | 4 |
| Phenyl[a] | 3 | 20 | 1 | 1 | 3 | 15 | 1 | 1 | 3 | 25 | 1 | 1 | 2 |

Abbreviations: AHS, Agricultural Health Study; IA, Iowa; Max, maximum; Min, minimum; NC, North Carolina.
[a]Summary statistics calculated only among users of chemicals in this group.
Allestimates are weighted to represent those who completed all AHS interviews and lived within the study region ($N = 3863$).
See Table 1 for chemical classifications.

likely to apply OPs than NC farmers (47% *vs* 43%: Phase 2, 47% *vs* 37%: Phase 3); however, in every phase, NC farmers applied OPs more days per year ($\text{median}_{\text{Phase1}} = 14$, $\text{median}_{\text{Phase2}} = 5$, and $\text{median}_{\text{Phase3}} = 10$) than IA farmers ($\text{median}_{\text{Phase1}} = 11$, $\text{median}_{\text{Phase2}} = 4$, and $\text{median}_{\text{Phase3}} = 5$). For all phases, the annual frequency of application of any OP ranged from $<5$ days to $>150$ days, with the majority of users applying OPs fewer than 20 days annually (Supplementary Figure 1). In Phase 1, the median frequency of use of individual OPs was between 2.5 and 7 days, corresponding to the two adjacent questionnaire categories of $<5$ days and 5–9 days (Table 4).

Use of specific OPs, on average, changed over time. Note that our results represent population changes, and not changes in use by specific individuals. Changes over time were not the same for all OPs. For example, secular trends were different for two OPs that were both commonly used in Phase 1, chlorpyrifos and malathion. The proportion of applicators using chlorpyrifos declined from 20% in Phase to 1–11% in Phase 3, while the proportion of applicators using malathion remained relatively constant over all three phases (18–19%). For terbufos, another OP commonly used at enrollment (17%), the proportion of users dropped to 5% by Phase 3. For fonofos, an OP which had its registration cancelled in 1999, use dropped from 5% in Phase 1 to essentially 0% by Phase 2. Conversely, tebupirimfos, a pesticide introduced in 1995, started at 5% prevalence in Phase 2 and increased to 9% in Phase 3.

Lifetime application days for all OPs was more variable than lifetime days for any individual OP (Table 5) because the numbers of OPs used differed among participants. For individual OPs, the minimum number of lifetime days applied ranged from 2.5 to 8.75 days, suggesting infrequent use or use in only one season. The median lifetime days for individual OPs ranged from 15 days for coumaphos to 53 days for acephate. The median lifetime days of all OPs (154 days) was similar to the highest 75th percentile among individual OPs (179 days for dichlorvos).

As seen in Figure 4, the lifetime days for individual OPs varied by state for some OPs, but not others. Of the 20 OPs, acephate, azinphos-methyl, and fenamiphos were used only in NC, whereas tebupirimfos was used only in IA. Of the remaining 16 OPs used in both states, median lifetime days of use were essentially the same (20 or 25 days) for seven OPs (dimethoate, disulfoton, ethoprop, fonofos, malathion, methyl parathion and tetrachlorvinphos), five had higher lifetime days in NC (diazinon, fenthion, phorate, phosmet, and ronnel), and four were used more among IA farmers (chlorpyrifos, coumaphos, dichlorvos, and terbufos). For some chemicals like malathion with similar median use in both states, differences became apparent at the 75th percentile (109 days for NC and 56 days for IA). While NC farmers had higher lifetime days for 8 of 20 individual OPs, the median lifetime days for all OPs combined was greater in IA (165 days) than NC (139 days), an observation attributable largely to NC farmers typically using fewer individual OPs than IA farmers.

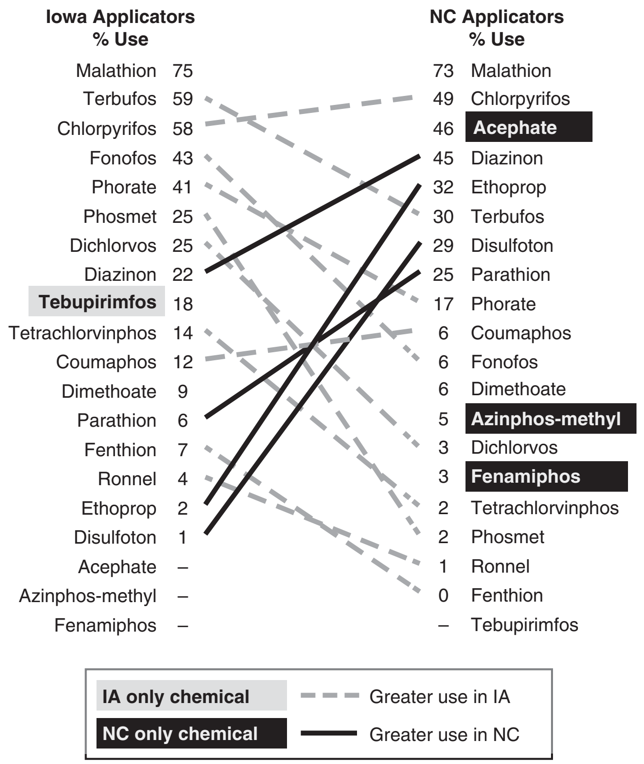


**Figure 3.** Rank order of organophosphorous insecticide use by state in the Agricultural Health Study. IA, Iowa; NC, North Carolina.

## DISCUSSION

Although there is much interest in the combined effects of OPs with regard to health, little is known about patterns of specific OP use by farmers. Using data from the AHS, we found that although almost all farmers had applied OPs sometime during their farming career; at the median, an individual had applied four OPs in his lifetime and at most 13 OPs. We observed regional differences, with some OPs being used exclusively in one state or another. The median number of days that users applied a specific OP was relatively constant across OPs. Thus, it is possible that the biggest determinant of a farmer's total annual days of OP exposure is the number of OPs used.

We observed changes over time in the OPs used consistent with nationwide trends. Chlorpyrifos and malathion remain among the most commonly used insecticides in agriculture. In US national estimates based on 2006–2007 data, chlorpyrifos was the most commonly used OP based on pounds of active ingredient used;[1] similarly in CA in 2008, chlorpyrifos was the most commonly used insecticide based on both pounds applied and acres treated.[4] In the United States, acephate was the second most commonly used OP in 2007; in CA, malathion was second based on pounds applied while dimethoate was second based on acres treated. In our Phase 3 data, based on use in 2005–2007, malathion was the most commonly used OP with 19% of the cohort applying it and chlorpyrifos was second with 11%. Although we lack data on pounds applied or acres treated, our relative ranking based on numbers of users in the AHS is comparable to these other metrics. The differences among data sources probably represent both regional differences in agricultural practices and crops grown, as well as data collection.

The AHS is a prospective cohort study of pesticide applicators that provides a unique opportunity to evaluate patterns of OP and other pesticide use over time. At enrollment, 82% of licensed pesticide applicators in NC and IA enrolled in the study; thus, our cohort is representative of private pesticide applicators in these two states. The response rate to the take-home questionnaire was lower, but previous analyses found few differences in demographic or farming characteristics between those who did or did not complete the take-home questionnaire.[14] Participants in this study completed not only the Phase 1 take-home questionnaire, but also the two follow-up interviews (Phases 2 and 3) and lived within specific geographic regions. Although our results are weighted to represent all participants who met the eligibility criteria, it is likely that our results are representative of most farmers who completed the most recent follow-up interview (Phase 3) given the similarity of our sample to this larger population with respect to age, farming, and pesticide use characteristics. The sampling frame for the neurological testing substudy was a random stratified sample of the cohort residing in specific geographic areas (eastern IA and Eastern NC). Generalizability to the whole cohort is probably very good, with the potential exception of farmers in western NC. Agriculture in NC has more regional heterogeneity in major crops than in IA; consequently, we may have missed exposure patterns unique to Christmas tree or apple production in western NC. However, farmers in western NC make up a small part of the overall cohort (8%), so we believe that the exclusion of farmers from this region would have little influence on the overall estimates.

We analyzed data from a stratified random sample of the cohort to estimate use of 27 different OPs by licensed private applicators in IA and NC. This sample represents a subset of the AHS cohort with enhanced OP assessment. There are two primary differences between these data and the data currently available for the full cohort: (1) information on OPs from the take-home checklist was included and lifetime days of use for these OPs was assigned based on the individual's use of other insecticides, and (2) unknown pesticides reported at Phases 2 and 3 were resolved to identify any additional OP use (detailed in online Supplement). Thus, these data provide a more complete picture of lifetime OP use than is currently available in the AHS as a whole. The main limitation of the AHS for assessment of lifetime OP use is that many of the commonly used OPs were ascertained on the take-home questionnaire (e.g., malathion and diazinon); thus, complete lifetime information is available only for those 44% who completed this questionnaire. In addition to the 10 OPs for which detailed information was collected during Phase 1, the take-home questionnaire also included a checklist of additional pesticides including 12 OPs, some of which are OPs commonly used in NC (i.e., acephate, ethoprop, and disulfoton). Although our sample represents a small portion of the AHS as a whole, by using a stratified random sampling method we were able to extrapolate the results of these enhanced OP data to a larger portion of the AHS.

One challenge to compiling lifetime use is that the data collection methods differed over the phases of the study. The Phase 1 questionnaire obtained defined responses about use of predetermined OPs, whereas in Phases 2 and 3 open-ended questions were used to obtain information about all pesticides used. Although the open-ended approach in Phases 2 and 3 provided the opportunity to include new OPs, we lost the ability to confirm true non-users (i.e., individuals who did not use that chemical). By having people who provide information on all chemicals they were currently using, we captured new OPs (e.g., tebupirimfos).

A major strength of this analysis is that these data reflect personal use of specific OPs by the same group of individuals at three time points. Farmers have been shown to provide reliable and reproducible reports of their pesticide use.[15–17] National estimates rely on sales figures or proprietary estimates of use[1] or state-specific crop surveys.[2] Our data reflect both temporal trends in pesticide use and changes in agricultural practices over time. These data, along with national and regional data, provide a better

**Table 4.** Annual days of OP application for three time periods for AHS participants (1993–2007).

| *OP* | *Phase 1 (1993–1997)* | | | | | | *Phase 2 (1999–2003)* | | | | | | *Phase 3 (2005–2007)*[a] | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *% Use in past year* | *Annual days* | | | | | *% Use in past year* | *Annual days* | | | | | *% Use in past year* | *Annual days* | | | | |
| | | *Min* | *25th percentile* | *Median* | *75th percentile* | *Max* | | *Min* | *25th percentile* | *Median* | *75th percentile* | *Max* | | *Min* | *25th percentile* | *Median* | *75th percentile* | *Max* |
| Annual OP days[b] | 68 | 1 | 5 | 13.5 | 21.75 | 207 | 45 | 1 | 2 | 4 | 9 | 122 | 42 | 1 | 3 | 6 | 13 | 153 |
| Acephate[c] | 15 | 1 | 2.5 | 7 | 8 | 39.5 | 10 | 1 | 2 | 4 | 8 | 26 | 10 | 1 | 4 | 8 | 14 | 30 |
| Azinphos methyl[c] | 2 | 2.5 | 2.5 | 7 | 7 | 29.5 | 0 | NR | | | | | 0 | NR | | | | |
| Chlorpyrifos | 21 | 2.5 | 2.5 | 7 | 7 | 49.5 | 12 | 1 | 1 | 2 | 4 | 14 | 11 | 1 | 2 | 4 | 7 | 20 |
| Coumaphos | 2 | 2.5 | 2.5 | 2.5 | 7 | 105 | 1 | 1 | 4 | 5 | 12 | 30 | 1 | 1 | 2 | 3 | 6 | 15 |
| Diazinon | 7 | 2.5 | 2.5 | 7 | 14.5 | 105 | 5 | 1 | 2 | 3 | 6 | 21 | 5 | 1 | 2 | 4 | 10 | 30 |
| Dichlorvos | 4 | 2.5 | 2.5 | 7 | 49.5 | 200 | 2 | 4 | 4 | 10 | 32 | 120 | 1 | 2 | 4 | 5 | 80 | 150 |
| Dimethoate[c] | 7 | 1 | 2.5 | 4.75 | 7 | 32 | 1 | 1 | 1 | 1 | 3 | 6 | 1 | 1 | 1 | 1 | 3 | 10 |
| Disulfoton[c] | 13 | 2.5 | 2.5 | 7 | 7 | 39.5 | 1 | 1 | 1 | 1 | 4 | 21 | 0 | NR | | | | |
| Fonofos | 5 | 2.5 | 2.5 | 7 | 7 | 29.5 | 0 | NR | | | | | 0 | NR | | | | |
| Malathion | 21 | 2.5 | 2.5 | 7 | 7 | 105 | 17 | 1 | 1 | 2 | 5 | 60 | 17 | 1 | 1 | 2 | 5 | 50 |
| Methyl parathion | 1 | 2.5 | 2.5 | 7 | 7 | 29.5 | 1 | 1 | 3 | 4 | 6 | 30 | 1 | 1 | 2 | 5 | 20 | 20 |
| Phorate | 2 | 2.5 | 7 | 7 | 14.5 | 29.5 | 1 | 1 | 2 | 5 | 8 | 15 | 1 | 2 | 5 | 10 | 10 | 30 |
| Phosmet[c] | 14 | 1 | 2.5 | 5 | 7 | 50 | 3 | 1 | 3 | 4 | 10 | 50 | 2 | 3 | 4 | 8 | 10 | 15 |
| Tebupirimfos | NM | | | | | | 4 | 1 | 2 | 4.5 | 7 | 17 | 8 | 1 | 3 | 5 | 7 | 30 |
| Terbufos | 16 | 2.5 | 2.5 | 7 | 14.5 | 29.5 | 8 | 1 | 2 | 3 | 7 | 20 | 6 | 1 | 5 | 7 | 10 | 30 |
| Tetrachlorvinphos[c] | 9 | 2 | 2.5 | 7 | 7 | 49.5 | 0 | NR | | | | | 0 | NR | | | | |

Abbreviations: AHS, Agricultural Health Study; Max, maximum; Min, minimum; OP, organophosphorous insecticide.
All estimates weighted to represent those who completed all AHS interviews and lived within the study region ($N = 3863$).
[a]Data collection period for this subset of participants.
[b]Based on the use of 27 possible OPs.
[c]For these OPs, frequency (days/year) was imputed for Phase 1 as these chemicals were reported on the take-home checklist: reported values may be overestimates as imputation assumed that all ever-users of the OP had used it in the past year.
NM = not on market; tebupirimfos was introduced in 1995. No Phase 1 use data were collected.
NR = not reported, chemical was used by $<1\%$ of sample.

**Table 5.** Lifetime days of OP use among participants in the AHS (1993–2007).

| OP | % Users | Minimum | 25th percentile | Median | 75th percentile | Maximum |
|---|---|---|---|---|---|---|
| All OPs | 95 | 2.5 | 68 | 154 | 362 | 8763 |
| Acephate | 21 | 2.5 | 21 | 53 | 116 | 501 |
| Azinphos methyl | 2 | 8.75 | 20 | 27 | 56 | 236 |
| Chlorpyrifos | 54 | 2.5 | 15 | 29 | 66 | 767 |
| Coumaphos | 10 | 2.5 | 9 | 15 | 56 | 1683 |
| Diazinon | 32 | 2.5 | 9 | 24 | 56 | 840 |
| Dichlorvos | 15 | 2.5 | 9 | 51 | 179 | 8680 |
| Dimethoate | 8 | 5 | 9 | 20 | 51 | 457 |
| Disulfoton | 14 | 2 | 17 | 25 | 56 | 236 |
| Ethoprop | 15 | 2.5 | 14 | 25 | 56 | 316 |
| Fenamiphos | 1 | 5 | 5 | 21 | 42 | 70 |
| Fenthion | 4 | 8.75 | 9 | 25 | 40 | 225 |
| Fonofos | 26 | 2.5 | 9 | 25 | 56 | 457 |
| Malathion | 74 | 2.5 | 9 | 25 | 66 | 2625 |
| Methyl parathion | 15 | 2.5 | 9 | 20 | 56 | 1628 |
| Phorate | 30 | 2.5 | 9 | 25 | 56 | 1628 |
| Phosmet | 15 | 2.5 | 14 | 25 | 56 | 600 |
| Ronnel | 3 | 2.5 | 9 | 20 | 51 | 225 |
| Tebupirimfos | 10 | 4 | 16 | 35 | 56 | 250 |
| Terbufos | 46 | 2.5 | 20 | 51 | 116 | 752 |
| Tetrachlorvinphos | 9 | 5.63 | 9 | 25 | 56 | 582 |

Abbreviations: AHS, Agricultural Health Study; OP, organophosphorous insecticide.
Allestimates weighted to represent those who completed all AHS interviews and lived within the study region ($N = 3863$).
Statistics calculated only for users of the pesticide.

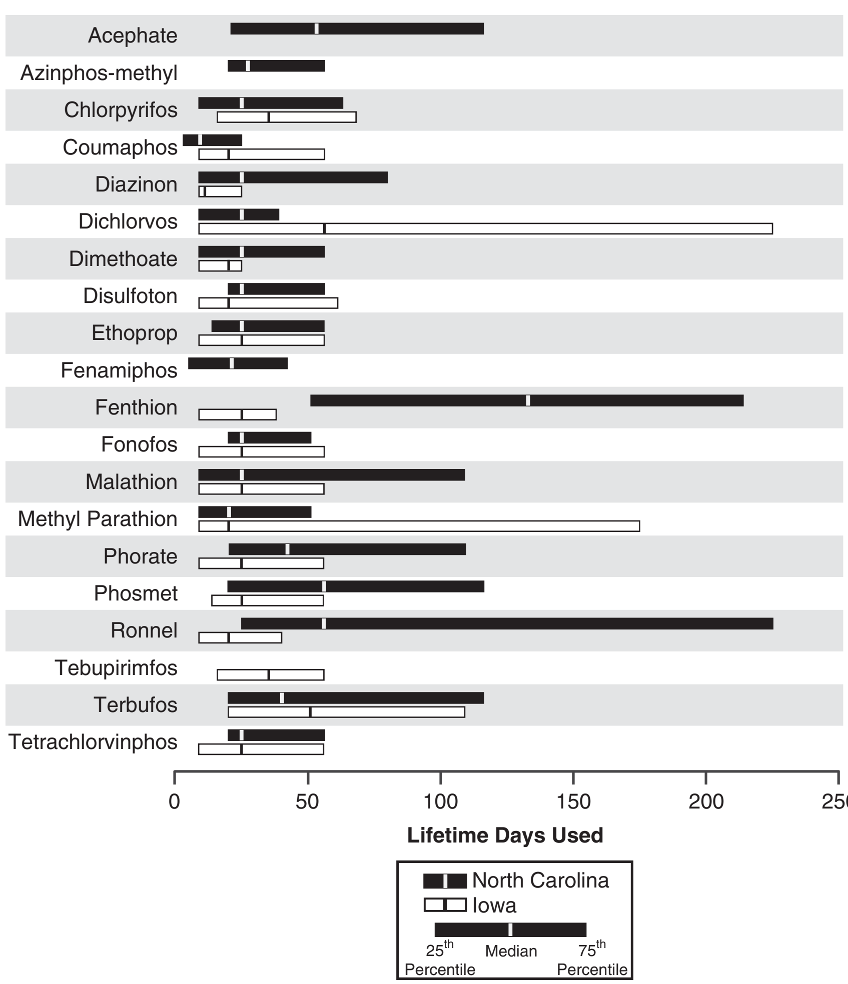


**Figure 4.** Lifetime days of 20 specific organophosphorous insecticides (OPs) stratified by state among private applicators in the Agricultural Health Study, 1993–2007.

understanding of use of OPs by individuals in agricultural settings. This information is critical not only for health assessments and epidemiology, but also for risk assessment and exposure characterization purposes.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

We thank Dr. Joe Coble for his efforts to create the AHS pesticide use data base. This work was supported by the intramural research program of the National Institutes of Health, the National Institute of Environmental Health Sciences (Z01-ES049030), National Cancer Institute (Z01-CP010119), and the National Institute for Occupational Safety and Health. The United States Environmental Protection Agency through its Office of Research and Development collaborated in the research described here; it has been subjected to Agency review and approved for publication.

### Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily reflect the views of the National Institute for Occupational Safety and Health and Health Canada.

## REFERENCES

1 United States Environmental Protection Agency (USEPA). *Pesticide Industry Sales and Usage: 2006 and 2007 Market Estimates*. Office of Pesticide Programs, US EPA, Washington, DC, 2011.

2 National Agricultural Statistics Service (NASS). Agricultural Chemical Use Database. http://www.pestmanagement.info/nass/app_usage.cfm, 2011. Accessed on 8 August 2011.

3 Gianessi L, and Reigner N. *Pesticide Use in the U.S. Crop Production: 2002*. CropLife Foundation, Crop Protection Research Institute, Washington, DC, 2006.

4 California Department of Pesticide Registration (CDPR). Pesticide Use Reporting. http://www.cdpr.ca.gov/docs/pur/purmain.htm, 2011. Accessed on 8 October 2011.

5 United States Environmental Protection Agency (USEPA). *Organophosphorus Cumulative Risk Assessment—2006 Update*. Office of Pesticide Programs, USEPA, Washington, DC, 2006.

6 Hodgson E, and Rose RL. Organophosphorus chemicals: potent inhibitors of the human metabolism of steroid hormones and xenobiotics. *Drug metab Rev* 2006: **38**(1–2): 149–162.

7 Mena S, Ortega A, and Estrela JM. Oxidative stress in environmental-induced carcinogenesis. *Mutat Res* 2009: **674**(1–2): 36–44.

8 Proskocil BJ, Bruun DA, Lorton JK, Blensly KC, Jacoby DB, Lein PJ, et al. Antigen sensitization influences organophosphorus pesticide-induced airway hyperreactivity. *Environ Health Perspect* 2008: **116**(3): 381–388.

9 United States Environmental Protection Agency (USEPA). *Organophosphate Pesticides: Revised Cumulative Risk Assessment*. Office of Pesticide Programs, USEPA, Washington, DC, 2002.

10 Barr DB, Bravo R, Weerasekera G, Caltabiano LM, Whitehead Jr RD, Olsson AO, et al. Concentrations of dialkyl phosphate metabolites of organophosphorus pesticides in the U.S. population. *Environ Health Perspect* 2004: **112**(2): 186–200.

11 Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. The Agricultural Health Study. *Environ Health Perspect* 1996: **104**(4): 362–369.

12 Starks SE, Gerr F, Kamel F, Lynch CF, Jones MP, Alavanja MC, et al. Neurobehavioral function and organophosphate insecticide use among pesticide applicators in the Agricultural Health Study. *Neurotoxicol Teratol* 2012: **34**(1): 168–176.

13 Wood A. Compendium of Pesticide Common Names. http://www.alanwood.net/pesticides/index.html, 2011. Accessed on 8 August 2011.

14 Tarone RE, Alavanja MC, Zahm SH, Lubin JH, Sandler DP, McMaster SB, et al. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am J Ind Med* 1997: **31**(2): 233–242.

15 Blair A, and Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology* 1993: **4**(1): 55–62.

16 Blair A, Tarone RE, Sandler D, Lynch CF, Rowland A, Wintersteen W, et al. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. *Epidemiology* 2002: **13**: 94–99.

17 Hoppin JA, Yucel F, Dosemeci M, and Sandler DP. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. *J Expo Anal Environ Epidemiol* 2002: **12**(5): 313–318.

Supplementary Information accompanies the paper on the Journal of Exposure Science and Environmental Epidemiology website (http://www.nature.com/jes)