Background: Melanoma rates continue to increase; however, few risk factors other than sun sensitivity and ultraviolet radiation (including sun exposure) have been identified. Although studies of farmers have shown an excess risk of melanoma and other skin cancers, it is unclear how much of this is related to sun exposure compared with other agricultural exposures.

Methods: We examined dose–response relationships for 50 agricultural pesticides and cutaneous melanoma incidence in the Agricultural Health Study cohort of licensed pesticide applicators, along with ever use of Older pesticides that contain arsenic. Logistic regression was used to examine odds ratios (ORs) and 95% confidence intervals (CIs) associated with pesticide exposure adjusted for age, sex, and other potential confounders.

Results: We found significant associations between cutaneous melanoma and manebe/mancozeb (25-63 exposure days: OR = 2.4; 95% CI, 1.2–4.9; trend p = 0.006), parathion (25-65 exposure days: OR = 2.4; 95% CI, 1.3–4.4; trend p = 0.003), and carbaryl (25-65 exposure days: OR = 1.7; 95% CI, 1.1–2.5; trend p = 0.013). Other associations with benomyl and ever use of arsenical pesticides were also suggested.

Conclusions: Most previous melanoma literature has focused on host factors and sex. Our research shows an association between several pesticides and melanoma, providing support for the hypotheses that agricultural chemicals may be another important source of melanoma risk.

Key Words: arsenic, farmers, melanoma, pesticides. Environ Health Perspect 118:812–817 (2010). doi:10.1289/ehp.0901518 [Online 17 February 2010]
take-home questionnaire in answering the question “What other pesticides have you used frequently (either now or in the past)? (Mark all that you have used).”

**Cohort follow-up.** Applicators were linked to cancer registry files in Iowa and North Carolina for case identification from enrollment (i.e., 1993–1997) through 31 December 2005 and to the state death registries and the National Death Index to ascertain vital status (Alavanja et al. 2005). This identified 271 incident cutaneous melanoma cases (hereafter referred to as melanoma) among 56,285 private and commercial applicators after exclusion of subjects with a nonmelanoma cancer diagnosis before enrollment. There were 150 cases of cutaneous melanoma diagnosed after enrollment among applicators without a nonmelanoma cancer diagnosis before enrollment who completed the take-home questionnaire (n = 24,704). This included two cases that also had a melanoa diagnosed before enrollment (to increase power). The average length of follow-up among the cohort was 10.3 years.

**Analyses.** Dose–response data available for pesticide use included total years of mixing or applying a specific pesticide, days per year of use for an average year, and decades of first use. Lifetime cumulative exposure days were calculated as application days per year × (total years of exposure). Lifetime exposure days were then weighted by an intensity score that accounts for pesticide application method and use of personal protective equipment (Dosemeci et al. 2002). Categorical variables were based on the distribution among cases: two exposure categories were created with near equal number of cases and by choosing cutoffs for days of use that correspond to weeks of use (e.g., < 70 days, ≥ 70 days). Only “ever use” data were available for arsenical pesticides (lead arsenate and inorganic and organic arsenc as defined on the questionnaire).

We used AHS data set release AHSREL0803.00 (available on request from AHS). Descriptive frequencies were used to compare cases and noncases regarding sun sensitivity, sun exposure, and obesity (based on body mass index). Unconditional logistic regression was used to examine associations between melanoma and pesticide exposure, adjusted for age categories and sex as well as other variables as indicated. Effect modification by current and past sun exposure (< 6 vs. ≥ 6 hr/day) was examined among pesticides showing a positive association with melanoma. We also examined potential confounding related to known melanoma risk factors, including hours of sun exposure (current and past), tendency to burn, natural red hair color, and body mass index (BMI). For ordered categorical factors, we also present odds ratios (ORs) and 95% confidence intervals (CIs) comparing the highest category with the reference category. To test for linear trend, we fitted a line to the β-coefficients for each category, assuming an equal increase in the ln(OR) for each category level (Breslow and Day 1980).

We limited final analyses to applicators completing the take-home questionnaire to allow for examination of potential confounding effects of melanoma risk factors [sun exposure, tendency to burn, hair color, and BMI, which were only available on the take-home questionnaire]. For the 22 pesticides detailed on the enrollment questionnaire, we compared results using the whole cohort with those for the restricted cohort who completed the take-home questionnaire. Minimal differences were seen.

**Results.** Overall, 271 incident melanoma cases were reported among all applicators. There were 150 incident melanomas among 24,704 applicators who completed the take-home questionnaire; this included two applicators diagnosed with melanomas both before and after enrollment. None of the controls had a reported melanoma before enrollment.

**Table 1.** Associations with cutaneous melanoma for sun sensitivity and sun exposure factors in the Agricultural Health Study among 24,704 pesticide applicators completing the take-home questionnaire.

| Sun sensitivity factors | Cases (n = 150) [n(%)] | Noncases (n = 24,554) [n(%)] | Minimally adjusted OR (95% CI) | Adjusted OR (95% CI) |
|-------------------------|-----------------------|-------------------------------|-------------------------------|---------------------|
| **Tendency to burn**    |                       |                               |                               |                     |
| No or mild sunburn      | 102 (69.4)            | 18,865 (78.0)                 | Reference                      | Reference           |
| Blistering or painful sunburn | 45 (30.6)         | 5,313 (22.0)                  | 1.50 (1.05–2.13)               | 1.23 (0.84–1.78)    |
| Missing                 | 3                     | 376                           |                               |                     |
| **Hair color**          |                       |                               |                               |                     |
| Black/brown/blonde      | 131 (88.5)            | 23,093 (96.9)                 | Reference                      | Reference           |
| Red                     | 17 (11.5)             | 744 (3.1)                     | 4.00 (2.39–6.66)               | 3.69 (2.16–6.32)    |
| Missing                 | 2                     | 717                           |                               |                     |
| **Eye color**           |                       |                               |                               |                     |
| Brown/green/hazel       | 77 (52.0)             | 12,535 (52.0)                 | Reference                      | Reference           |
| Blue/gray               | 71 (48.0)             | 11,568 (48.0)                 | 0.92 (0.66–1.26)               | 0.85 (0.61–1.19)    |
| Missing                 | 2                     | 451                           |                               |                     |
| **Sun exposure** (hours per day spent in the sun during growing season) | | | | |
| At enrollment (1993–1997) |                       |                               |                               |                     |
| ≤ 2 hr/day              | 12 (8.1)              | 2,522 (10.5)                  | Reference                      | Reference           |
| 3–5 hr/day              | 49 (33.1)             | 6,085 (27.8)                  | 1.56 (0.83–2.94)               | 1.56 (0.82–2.95)    |
| 6–10 hr/day             | 72 (48.7)             | 11,157 (46.3)                 | 1.39 (0.75–2.56)               | 1.38 (0.74–2.56)    |
| > 10 hr/day             | 15 (10.1)             | 3,701 (15.4)                  | 1.00 (0.46–2.13)               | 1.04 (0.48–2.24)    |
| Missing                 | 2                     | 489                           |                               |                     |
| 10 years before enrollment |                       |                               |                               |                     |
| ≤ 2 hr/day              | 6 (4.3)               | 1,392 (6.2)                   | Reference                      | Reference           |
| 3–5 hr/day              | 24 (17.0)             | 4,366 (19.4)                  | 1.37 (0.56–3.37)               | 1.40 (0.57–3.45)    |
| 6–10 hr/day             | 81 (57.4)             | 11,670 (51.8)                 | 1.56 (0.68–3.58)               | 1.54 (0.66–3.54)    |
| > 10 hr/day             | 30 (21.3)             | 5,091 (22.6)                  | 1.27 (0.53–3.07)               | 1.31 (0.54–3.16)    |
| Missing                 | 9                     | 2,035                         |                               |                     |

**Obesity**

| BMI at 20 years of age | Cases (n = 150) [n(%)] | Noncases (n = 24,554) [n(%)] | Minimally adjusted OR (95% CI) | Adjusted OR (95% CI) |
|------------------------|-----------------------|-------------------------------|-------------------------------|---------------------|
| ≥ 20 kg/m²             | 9 (7.0)               | 2,997 (13.9)                  | Reference                      | Reference           |
| ≥ 20–24.99 kg/m²       | 72 (56.3)             | 12,330 (57.0)                 | 2.19 (1.09–4.39)               | 2.16 (1.07–4.33)    |
| ≥ 25 kg/m²             | 47 (36.7)             | 6,295 (28.1)                  | 3.38 (1.64–6.94)               | 3.39 (1.65–6.97)    |
| Missing                | 22                    | 2,932                         |                               |                     |

*Adjusted for age at enrollment and sex. *AAdjusted for age at enrollment, sex, tendency to burn, and red hair, unless one of these factors is being evaluated, in which case adjustment is limited to the remaining three factors.
insecticides, or organophosphate insecticides (data not shown). Melanoma risk showed a dose–response association with carbamate pesticides overall (trend \( p = 0.032 \); data not shown because this was the result of the associations with carbaryl and benomyl, two of the four carbamate pesticides). Table 2 reports the four specific pesticides that showed a dose–response association with melanoma among applicators. All four pesticides had detailed dose information only on the take-home questionnaire; thus, results in Table 2 are restricted to the take-home questionnaire. None of the 22 pesticides detailed on the enrollment questionnaire was associated with melanoma, compared with 4 of the 28 pesticides detailed on the take-home questionnaire. In an analysis of the 22 pesticides from the enrollment questionnaire, which we restricted to applicators that also completed the take-home, results were similarly negative (data not shown). Although overall fungicide use did not appear to be related to melanoma, two of six fungicides, benomyl and maneb/mancozeb, had significant dose–response associations with melanoma. We also found increased ORs for two insecticides (carbaryl and parathion). Among the cohort members, exposure to carbon tetrachloride was uncommon, with only two cases reporting > 7 days of application over their lifetime. We found no associations with the organochlorine pesticides aldrin, chlordane, dieldrin, dichlorodiphenyltrichloroethane (DDT), heptachlor, lindane, or toxaphene. We found no effect modification of the association with pesticides by sun exposure.

We specifically examined pesticides with arsenic content (Table 3). The crude OR for ever versus never use of lead arsenate was 2.1 (95% CI, 1.1–3.9), but after adjusting for age and sex, ever use of lead arsenate insecticide was not associated with melanoma risk. Ever use of inorganic arsenic herbicides showed a significant association with cutaneous melanoma, but only 44 applicators reported use (OR = 5.4; 95% CI, 1.3–22.9; adjusted for age and sex). None of the few applicators who reported use of organic arsenic herbicides was a melanoma case (data not shown). Exposure to any of these three arsenical pesticides was associated with melanoma similar to lead arsenate (Table 3).

Table 2. Associations between cutaneous melanoma and pesticides for 150 melanoma cases within 24,704 pesticide applicators completing the take-home questionnaire in the Agricultural Health Study.

| Intensity-weighted lifetime days of exposure | Cases [n(%)] | Remaining cohort [n(%)] | OR (95% CI)a |
|---------------------------------------------|-------------|-------------------------|--------------|
| Benomyl (fungicide)b                      |             |                         |              |
| No exposure                                | 131 (91.0)  | 21,699 (93.1)            | 1.0          |
| < 133 exposure-days                        | 7 (4.9)     | 1,194 (5.1)              | 1.0 (0.4–2.2)|
| ≥ 133 exposure-days                        | 6 (4.2)     | 419 (1.8)                | 2.8 (1.2–6.5)|
| Missing                                    | 6           | 1,242                   |              |
| Trend p-value                              |             |                         | \( p = 0.061 \) |
| Carbaryl (insecticide)b                   |             |                         |              |
| No exposure                                | 64 (46.7)   | 13,570 (60.3)            | 1.0          |
| < 56 exposure-days                         | 37 (26.4)   | 5,001 (22.2)             | 1.3 (0.9–2.1)|
| ≥ 56 exposure-days                         | 39 (27.9)   | 3,939 (17.5)             | 1.7 (1.1–2.5)|
| Missing                                    | 10          | 2,044                   |              |
| Trend p-value                              |             |                         | \( p = 0.013 \) |
| Maneb/mancozeb (fungicide)c               |             |                         |              |
| No exposure                                | 127 (88.2)  | 21,783 (92.9)            | 1.0          |
| < 63 exposure-days                         | 8 (5.6)     | 947 (4.0)                | 1.6 (0.8–3.4)|
| ≥ 63 exposure-days                         | 9 (6.2)     | 713 (3.0)                | 2.4 (1.2–4.9)|
| Missing                                    | 6           | 1,101                   |              |
| Trend p-value                              |             |                         | \( p = 0.006 \) |
| Parathion (ethyl or methyl) (insecticide)  |             |                         |              |
| No exposure                                | 122 (85.3)  | 21,730 (93.1)            | 1.0          |
| < 56 exposure-days                         | 10 (7.0)    | 899 (4.0)                | 1.6 (0.8–3.1)|
| ≥ 56 exposure-days                         | 11 (7.7)    | 709 (3.0)                | 2.4 (1.3–4.4)|
| Missing                                    | 7           | 1,216                   |              |
| Trend p-value                              |             |                         | \( p = 0.003 \) |

Table 2. Associations between cutaneous melanoma and pesticides for 150 melanoma cases within 24,704 pesticide applicators completing the take-home questionnaire in the Agricultural Health Study.

| Arsenicd | Exposed [n(%)] | OR (95% CI) |
|----------|----------------|-------------|
| Lead arsenate crop insecticide             |               |             |
| Never used                                  | 140 (93.3)    | 23,733 (96.7) |               |
| Ever used                                   | 10 (6.7)      | 821 (3.3)    | 2.1 (1.1–3.9) | 1.2 (0.6–2.3) |
| Any arsenic pesticidec                      |               |             |
| Never used                                  | 139 (82.7)    | 23,680 (96.4) |               |
| Ever used                                   | 11 (7.3)      | 874 (3.6)    | 2.2 (1.2–4.1) | 1.3 (0.7–2.4) |

Table 3. Arsenical pesticide exposure and 150 cutaneous melanomas among 24,704 pesticide applicators completing the take-home questionnaire in the Agricultural Health Study.

Table 4. Interactions of lead arsenate and specific pesticides on risk of cutaneous melanoma among pesticide applicators completing the take-home questionnaire in the Agricultural Health Study.

| Pesticide/exposure | All subjects | Not exposed to lead arsenate | Exposed to lead arsenate | p-Value for interactionc |
|--------------------|--------------|-----------------------------|--------------------------|--------------------------|
| Benomylfungicide    | Cases/nocases \( a \) | OR (95% CI) | Cases/nocases \( a \) | OR (95% CI) | Cases/nocases \( a \) | OR (95% CI) | p-Value for interactionc |
| No exposure                              | 131/21,699       | 1.0 (reference) | 128/21,110       | 1.0 (reference) | 3/589          | 1.0 (reference) |                   |
| Any exposure                             | 13/1,613         | 1.2 (0.7–2.1)   | 7/1,440          | 0.7 (0.3–1.6)   | 6/173          | 6.7 (1.6–27.0)  | \( p = 0.006 \) |
| Carbaylfungicide                           |               |               |               |               |               |               |                   |
| No exposure                              | 64/13,570        | 1.0 (reference) | 63/13,444       | 1.0 (reference) | 1/126          | 1.0 (reference) |                   |
| Any exposure                             | 76/8,940         | 1.5 (1.0–2.0)   | 67/8,309        | 1.4 (1.0–2.0)   | 9/621          | 1.8 (0.2–14.4)  | \( p = 0.835 \) |
| Maneb/mancozebfungicide                   |               |               |               |               |               |               |                   |
| No exposure                              | 127/21,793       | 1.0 (reference) | 125/21,235      | 1.0 (reference) | 2/558          | 1.0 (reference) |                   |
| Any exposure                             | 17/1,660         | 1.5 (0.9–2.5)   | 9/1,457         | 0.9 (0.5–1.8)   | 8/203          | 10.8 (2.3–51.3) | \( p = 0.005 \) |
| Parathion (insecticide)                   |               |               |               |               |               |               |                   |
| No exposure                              | 122/21,730       | 1.0 (reference) | 120/21,238      | 1.0 (reference) | 2/492          | 1.0 (reference) |                   |
| Any exposure                             | 21/1,608         | 1.9 (1.2–3.0)   | 13/1,331        | 1.5 (0.8–2.7)   | 8/277          | 7.3 (1.5–34.6)  | \( p = 0.065 \) |

Table 4. Interactions of lead arsenate and specific pesticides on risk of cutaneous melanoma among pesticide applicators completing the take-home questionnaire in the Agricultural Health Study.

\( a \)Adjusted for age and sex. Trend \( p \)-values were for linear trend in continuous or categorical variables.

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between melanoma and the pesticides shown in Table 2. Two were significantly modified by use of lead arsenate crop insecticide, whereas parathion was nonsignificantly modified. For all three pesticides (benomyl, maneb/ mancozeb, and parathion), we found higher ORs for melanoma (ORs > 6.0) among those who had used arsenical pesticides. These effects could not be explained by age. The carbaryl and melanoma association showed no modification by lead arsenate.

**Discussion**

In this study we examined melanoma risk in relation to occupational exposure to pesticides among pesticide applicators in Iowa and North Carolina. The chemical subcohort approach, used in other reports, provides information on all (cancer) outcomes associated with a specific chemical and allows the AHS to provide dose–response information that may inform future risk assessments. The case–control approach used here allows us to consider all factors, not just chemicals, associated with a specific cancer such as melanoma. The AHS pesticide applicators were not shown to be at an increased risk of melanoma relative to populations of these two states (Alavanja et al. 2005), but additional evaluations of melanoma are warranted in light of previous literature. Commonly reported risk factors such as sun sensitivity and sun exposure (Dennis et al. 2008) were associated with melanoma in this cohort.

The strongest pesticide associations were with maneb/mancozeb (a dithiocarbamate fungicide) and parathion (an ethyl or methyl insecticide). In addition, dose–response relationships were seen for two (benomyl and carbaryl) of four different carbamate pesticides. Our carbaryl finding supports a previous report from a prospective analysis of carbaryl applicators in this cohort (Mahajan et al. 2007) with 2 additional years of follow-up (36 additional cases among those completing the take-home questionnaires). Another previous report that focused on organochlorine insecticides within the cohort noted an association between melanoma and toxaphene for lifetime exposure but not for intensity-weighted lifetime days of exposure (Purdue et al. 2006), a measure that takes into account factors such as protective clothing that may modify exposure. We did not see an association with melanoma cases diagnosed through 2005 and toxaphene for intensity-weighted lifetime days of exposure. The data suggested a possible association between melanoma and arsenical pesticides. Although arsenic exposure was limited, arsenical pesticides appeared to modify the effect of benomyl and maneb/mancozeb pesticides independent of age.

The hypothesis that melanoma may be related to pesticides stems from the relationships among epidermal melanocytes, nevi, and the development of melanoma. Dermatitis related to pesticide exposure was described in 1921 (McCord et al. 1921). Other skin diseases or irritations related to pesticides have been reported, including a case report of erythema multiforme related to parathion (Spiewak 2001). A review of 12 studies of farmers found that 8 showed an excess risk of melanoma (7 for other nonmelanoma skin cancers) (Blair and Zahm 1991; Spiewak 2001), but it is unclear how much of this is related to sun exposure compared with pesticides or other exposures. A study of white Ranch Hand Vietnam veterans found an increased risk of melanoma related to dioxin exposure and herbicide exposure (Akkhar et al. 2004). An additional report of an increased standardized incidence ratio for melanoma among Pan Britannica Industry’s pesticide factory workers suggests that pesticides are related to the development of melanoma (Wilkinson et al. 1997). A more recent study found an association with cutaneous melanoma and a longer duration of residential pesticide use (Fortes et al. 2007). They found that the most common compounds for indoor pesticides used in these residents included pyrethroids and carbamates. Additional evidence has shown that pesticides, carbon tetrachloride, and formaldehyde are related to increased risk of intraocular melanoma (Holly et al. 1996). We had too few cases of intraocular melanoma to examine this association.

We did not find other analytic studies that have reported an association with maneb/mancozeb or parathion and melanoma. In this large cohort of pesticide applicators, we only found about 7% of applicators had applied these pesticides; thus, the exposure rate in the general population is likely to be low. However, a study of banana plantation workers in Costa Rica reported an increased standardized incidence ratio for melanoma (Wesseling et al. 1996). Chemicals used on bananas include maneb, mancozeb, and benomyl, along with dibromochloropropane, chlorothalonil, and formaldehyde (Wesseling et al. 1996). They saw that the risk of melanoma also increased with the number of years of employment at banana plantations. This provides further evidence of the potential association between melanoma and maneb/mancozeb and benomyl. For parathion, we did not find any study directly linking it with melanoma. Nevertheless, a laboratory study of sunscreen found that those containing the physical ultraviolet absorbers titanium dioxide or zinc oxide enhance the transdermal absorption of parathion (Brand et al. 2003). In our study, when we further adjusted levels of parathion associated with melanoma for sunscreen use, we found no differences in the ORs. However, applicators were not asked about the details on types of sunscreen used or frequency or duration of use.

A link between arsenic and cancers of the bladder and lung and nonmelanoma skin cancer is well established. An association between arsenic and melanoma has only been reported in one other study to date, with an OR of 2.1 (95% CI, 1.4–3.3) for the highest quartile of toenail arsenic content (Beane Freeman et al. 2004). Our data support the possible association between melanoma and arsenic that is not explained by age, but the data are limited by the rarity of exposure and lack of assessment of frequency or duration of exposure. The mechanistic pathways of arsenical carcinogenesis may include oxidative stress (An et al. 2004; Shi et al. 2004), ultraviolet enhanced mutagenicity (Chen et al. 2006; Rossman 2003), and genotoxicity or altered DNA repair (Huang et al. 1995; Koehler et al. 1996; Mahata et al. 2003). Arsenic may also work by an epigenetic mechanism that changes the function of the DNA without affecting the normal DNA sequence. Although many arsenical compounds have been discontinued in the United States, arsenical pesticides are still widely available in some countries, and some farms have leftover supplies that continue to represent some potential risk (Reigart and Roberts 1999). Several studies of humans have shown an association between nonmelanoma skin cancer and heavy arsenic exposure via drugs, drinking water with a high arsenic content, or the occupational environment (Chen et al. 1985; Guo et al. 2001; Hsueh et al. 1995, 1997; International Agency for Research on Cancer 1998; Karagas et al. 2001; Pesch et al. 2002; Tseng 1977). Most published studies examining arsenic exposure and skin cancer risk originate from Taiwan, Bangladesh, or China. Among these studies, only one specifically mentioned examining melanoma and did not find an association (Guo et al. 2001); however, melanoma is rare in Chinese populations. An interaction has been demonstrated in one cross-sectional study where the risk of skin lesions associated with various levels of arsenic exposure was greater in those with excessive sun exposure (Chen et al. 2006). We did not see an interaction with sun exposure in our data, but we had limited power to examine this.

The AHS has several strengths, including a prospective design, comprehensive pesticide exposure assessment, completeness of follow-up, and high participation rates. Previous analyses have shown that AHS applicators completing the take-home questionnaire were similar to those who completed only the enrollment questionnaire, with the exception that those completing the take-home questionnaire tended to be older (Tarone
Appendix 1. Pesticide frequency and duration data evaluated for associations with melanoma within the Agricultural Health Study, 1993–1997.

| Category/questionnaire | Herbsicides | Enrollmnt | Take-home |
|-------------------------|-------------|-----------|-----------|
|                         | Alachlor, atrazine, cyanazine, dicamba, 2,4-D, EPTC, glyphosate, imazethapyr, metolachlor, trifluralin | Butylate, chlorimuron-ethyl, metribuzin, paraquat, pendimethalin, petroleum oil as herbicide, 2,4-A-T, 2,4-A-TP | 
|                         | Fungicides | Enrollmnt | Take-home |
|                         | Captan, chlorothanil, ziram | Benomyl, maneb/mancozeb, metalaxyl | Methyl bromide |
|                         | Fumigants | Enrollmnt | Take-home |
|                         | Methyl bromide | Aluminum phosphide, ethylene dibromide, carbon tetrachloride/carbon disulfide |

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; EPTC, S-ethyl dipropylthiocarbamate.

et al. 1997). Our analyses (data not shown) of melanoma in association with pesticides detailed on the enrollment questionnaire showed magnitudes for all who completed the enrollment questionnaire similar to those when such analyses were restricted to subjects who also completed the take-home questionnaire. A comparison of the incident cutaneous melanoma cases reported in the overall cohort (those completing the enrollment questionnaire) and those who completed the enrollment and the take-home questionnaire showed similar distributions by histologic site and body site (Dennis et al. 2008). Additionally analyses showed ORs similar to other studies for known sun sensitivity risk factors for melanoma. A limitation of this study was the small number of subjects who applied some of the pesticides, thus limiting the power of some analyses at this time.

Sun exposure, perhaps the strongest risk factor for melanoma, is difficult to capture via questionnaire. Because farmers spend a great deal of time in the sun, we cannot rule out the possibility that these pesticides–specific results are driven by sun exposure. However, results deferred for pesticides within a specific class, and within the limits of small numbers, were similar in Iowa and North Carolina. Furthermore adjusting for owning the farm or farm size (which might affect time outdoors) did not alter these findings. In addition, we had insufficient information on lifelong crop patterns to assess confounding by other factors potentially related to growing orchard fruits where arsenical pesticides were historically used. Finally, multiple comparisons may be an issue because we initially evaluated 50 pesticides. However, we initially focused on associations at the ≥ 0.01 significance level in the crude analyses (data not shown) and considered biologic plausibility. These results should also be interpreted with regard to their consistency with other studies.

Conclusions

Increased cutaneous melanoma risk was seen among applicators who had used/applied maneb/mancozeb and parathion, and potentially benomyl as well as lead arsenate, compared with never users of these products. The results are consistent with prior findings of an association between melanoma and arsenic. We observed a significant effect modification when benomyl and maneb/mancozeb users were also exposed to lead arsenate. In addition, our previous observation in the AHS of an association between carbaryl and melanoma was upheld when we added 2 additional years of cases. Most of the previous melanoma literature has focused on host factors and sun exposure, but our study suggests more research is needed on chemicals and other environmental factors that may increase the risk of cutaneous melanoma.

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