Lifetime Pesticide Use and Monoclonal Gammopathy of Undetermined Significance in a Prospective Cohort of Male Farmers

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BACKGROUND: Farmers have a higher incidence of multiple myeloma, and there is suggestive evidence of an elevated prevalence of its precursor, monoclonal gammopathy of undetermined significance (MGUS), relative to the general population. Pesticide exposures are suspected to play a role; however, the biologic plausibility for associations with multiple myeloma remains unclear.

OBJECTIVES: Our objectives were to examine the prevalence of MGUS and evaluate associations with a wide range of pesticides in a large sample of farmers.

METHODS: We obtained sera and assessed MGUS among 1,638 male farmers ≥50 years of age in the Agricultural Health Study (AHS), a prospective cohort in Iowa and North Carolina. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed to estimate associations with MGUS for recent use (within the 12 months before phlebotomy) and cumulative intensity-weighted lifetime days of use of specific pesticides.

RESULTS: The age-standardized MGUS prevalence was significantly elevated among AHS farmers (7.7%) compared with demographically similar men in the National Health and Nutrition Examination Survey (2.8%) or Olmsted County, Minnesota (3.8%; p < 0.001). Recent use of permethrin was associated with MGUS [recent use vs. no recent use, OR = 1.82 (95% CI: 1.06, 3.13)], especially among those who had also used it in the past [recent and past use vs. never use, OR = 2.49 (95% CI: 1.32, 4.69)]. High intensity-weighted lifetime use of the organochlorine insecticides aldrin and dieldrin was associated with MGUS relative to those who never used either of these pesticides [OR = 2.42 (95% CI: 1.29, 4.54); p_trend = 0.006]. We also observed a positive association with high lifetime use of petroleum oil/distillates as an herbicide, as well as an inverse association with fonofos use.

DISCUSSION: This is the largest investigation of MGUS in farmers and the first to identify an association with MGUS for permethrin, a pyrethroid insecticide previously associated with multiple myeloma. Given the continued widespread use of permethrin in various residential and commercial settings, our findings may have important implications for exposed individuals in the general population.

Introduction

An excess in the incidence of multiple myeloma (MM), an aggressive plasma cell malignancy, has been consistently observed in studies of farmers and other agricultural workers conducted over the past several decades (Perrotta et al. 2008). In the Agricultural Health Study (AHS), a prospective cohort that includes licensed pesticide applicators in Iowa and North Carolina, the incidence of MM is elevated among farmers relative to the general population in those states (Alavanja et al. 2005; Koutros et al. 2010; Lerro et al. 2019). Similar findings have been observed in the AGRiculture and CANcer (AGRICAN) study in France and among workers in the agricultural sector in Sweden (Lemarchand et al. 2017; Lope et al. 2008). The reasons for the excess of MM in farmers remain unclear, but exposure to pesticides is suspected to play a role (Lemarchand et al. 2017; Lope et al. 2008; Perrotta et al. 2008, 2013; Tual et al. 2019). Prior investigations in the AHS have noted significant exposure–response trends with MM risk for increasing exposure to the pyrethroid insecticide permethrin (Alavanja et al. 2014; Rusiecki et al. 2009), and several organochlorine insecticides have been associated with increased risk of lymphoid malignancies (a classification that includes MM) (Alavanja et al. 2014).

MM is nearly always preceded by a largely asymptomatic condition known as monoclonal gammopathy of undetermined significance (MGUS) (Landgren et al. 2009b), which is typically characterized by detection of a monoclonal (M)-protein in serum (Rajkumar et al. 2014). Consistent with the reported excess of MM in the AHS and other farming populations, an elevated prevalence of MGUS was previously observed among 555 AHS male pesticide applicators ≥50 years of age (Landgren et al. 2009a). To follow up on this observation, we conducted a larger investigation of MGUS in the Biomarkers of Exposure and Effect in Agriculture (BEEA) study (Hofmann et al. 2015), a subcohort within the AHS (Alavanja et al. 1996). Our investigation included approximately three times as many participants as the previous AHS investigation of MGUS. This allowed us to estimate the prevalence of MGUS in this population with greater precision and, importantly, to investigate associations with specific
pesticides for MGUS both overall and for the non-IgM subtypes that most commonly progress to MM. In this study, we were motivated to understand the biologic plausibility of observed associations with MM and to provide new insights into how specific pesticides may influence the development of MM and other lymphoid malignancies.

Methods

Study Population

The design and methodology of BEEA, a longitudinal observational study with collection of biospecimens from a subset of AHS participants, have been described previously (Hofmann et al. 2015). Briefly, between 2010–2017 we enrolled 1,681 male pesticide applicators ≥50 years of age who resided in Iowa or North Carolina, were never diagnosed with cancer (except nonmelanoma skin cancer), and completed questionnaires administered at AHS enrollment (1993–1997) and two follow-up interviews (1999–2003, 2005–2010). The BEEA study protocol was approved by institutional review boards at the National Cancer Institute and other participating institutions, and all BEEA participants provided written informed consent.

Laboratory Measurements

Serum specimens were assayed consecutively in the Protein Immunology Laboratory at Memorial Sloan Kettering Cancer Center. Samples were first tested by capillary electrophoresis to ascertain the occurrence and pattern of M-protein bands; those with an observed band or suspicious patterns were tested by serum immunofixation to confirm MGUS and to determine the heavy- and light-chain isotypes. Similar analytical methods were used in the prior AHS investigation (Landgren et al. 2009a) and other population-based studies (Kyle et al. 2006; Landgren et al. 2014, 2015, 2018). Assay results were reviewed in a blinded fashion by two of the authors (K.M. and O.L.). Results for blinded duplicate quality control samples from 60 participants (including 7 with MGUS) were 100% concordant for MGUS status and isotype. Blood samples were unavailable for 20 BEEA participants, and samples from 23 participants could not be tested due to preanalytical issues (e.g., lipemia, hemolysis), leaving 1,638 participants with laboratory results for analysis.

Pesticide Exposure Assessment

We estimated cumulative intensity-weighted lifetime days of occupational use of specific pesticides based on information reported on the AHS enrollment questionnaire and two subsequent follow-up questionnaires that were completed by all BEEA participants, as well as an additional take-home questionnaire from the AHS enrollment soliciting detailed information on a subset of pesticides not collected in the enrollment questionnaire (completed by 62% of BEEA participants). All questionnaires are available https://aghealth.nih.gov/collaboration/questionnaires.html. Intensity-weighted lifetime days were estimated by multiplying lifetime days by an intensity-weighting score that accounts for factors that may influence exposure, including application method, mixing pesticides, repairing spray equipment, and use of personal protective equipment (Coble et al. 2011). We evaluated associations with MGUS for intensity-weighted lifetime occupational use of 36 pesticides (16 insecticides, 17 herbicides, 2 fungicides, and 1 fumigant) for which we had detailed exposure information and ≥10 exposed MGUS cases. Exposure to each pesticide was categorized as follows based on the overall distribution of intensity-weighted lifetime days of use among exposed participants, with never users as the referent group: a) in quartiles for three pesticides with ≥80 exposed MGUS cases; b) in tertiles for six pesticides with 60–79 exposed cases; and c) as above or below the median number of intensity-weighted lifetime days for the remaining 27 pesticides. Because aldrin and dieldrin are structurally similar and aldrin is quickly converted to dieldrin in the environment and in vivo after exposure (ATSDR 2002), we assessed intensity-weighted lifetime days of use of aldrin and dieldrin combined. To follow up on prior findings of associations with MGUS for the fumigant mixture carbon tetrachloride/carbon disulfide and the fungicide chlorothalonil (Landgren et al. 2009a), we characterized exposure to these pesticides based on ever use (compared with never users) because there were <10 exposed MGUS cases with information on intensity-weighted lifetime days of use of each (carbon tetrachloride/carbon disulfide, n = 7; chlorothalonil, n = 6).

Information on recent pesticide use (in the last 12 months) was ascertained at BEEA enrollment/specimen collection (Hofmann et al. 2015). Of the 36 pesticides that we evaluated, there were 5 (2 insecticides and 3 herbicides) with ≥10 recently exposed MGUS cases. To assess whether the timing of exposure to these selected pesticides might influence MGUS development, we assessed associations separately for recent use (recently used vs. not recently used) and combined with past use from all previously administered questionnaires (never, past use only, both past and recent use). We also evaluated associations with intensity-weighted lifetime use of these 5 pesticides after excluding those with recent use only.

Statistical Analysis

Estimates of MGUS prevalence were age-standardized to the U.S. population of White males ≥50 years of age based on the 2000 census (U.S. Census Bureau 2001). We compared age-specific and age-standardized MGUS prevalence in BEEA with those observed among demographically similar individuals (males ≥50 years of age, 97.3% White) in Olmsted County, Minnesota, for the years 1995–2001 (Kyle et al. 2006), and in White males ≥50 years of age from a nationally representative sample of the U.S. population from the National Health and Nutrition Examination Survey (NHANES) for the years 1988–1994 and 1999–2004 (Landgren et al. 2014).

We computed odds ratios (ORs) and 95% confidence intervals (CIs) for associations of MGUS with specific pesticides using logistic regression models adjusted for age (50–59, 60–69, 70–79, and ≥80 years) and state of residence (Iowa, North Carolina). We also performed analyses further adjusting for other pesticides that were statistically significantly associated with MGUS in this sample in an exposure–response manner (p_trend < 0.05; aldrin/dieldrin, petroleum oil/distillates, and fonofos) or with recent use (permethrin). Trend tests were conducted by modeling the within-category median values for intensity-weighted lifetime days as continuous variables. Because IgM MGUS typically progresses to Waldenström macroglobulinemia or other lymphoid malignancies rather than MM (Kyle et al. 2018; Rajkumar et al. 2014), we also conducted analyses restricted to non-IgM MGUS.

In secondary analyses, we pooled data from the BEEA study and the previous study of MGUS in the AHS (Landgren et al. 2009a) to further evaluate MGUS prevalence and associations with lifetime pesticide use in a larger sample of male farmers. All participants in BEEA and 555 participants in the prior AHS study were ≥50 years of age; our pooled sample was restricted to those ≥50 years of age. Among the 1,638 BEEA participants tested for MGUS and the 555 participants from the prior study, there were 144 individuals who participated in both studies. For these 144 overlapping participants, we selected the data from BEEA only for inclusion in the pooled analyses. The pooled data set included a combined total of 2,049 participants (1,638 from BEEA and 411 from the prior AHS study). We estimated the prevalence of
Table 1. Selected characteristics [reported as frequency (%) unless otherwise noted] of BEEA participants by MGUS status.

| Characteristic | MGUS | No MGUS | p-Value |
|----------------|------|---------|---------|
| Overall        | 129  | 1,509   |         |
| Age at blood draw (y) [median (IQR)] | 69 (62–78) | 64 (57–72) | <0.001* |
| 50–59          | 23 (18) | 502 (33) |         |
| 60–69          | 42 (33) | 537 (36) |         |
| 70–79          | 44 (34) | 380 (25) |         |
| ≥80            | 20 (16) | 90 (6)  |         |
| State          |       |         | 0.06*   |
| Iowa           | 91 (71) | 1,174 (78) |       |
| North Carolina | 38 (29) | 335 (22)  |         |
| Race           |       |         | 0.52*   |
| White          | 128 (99) | 1,475 (98) |       |
| Black          | 1 (1)  | 13 (1)  |         |
| Other/missing  | 0 (0)  | 21 (1)  |         |
| MGUS isotype   |       |         |         |
| IgG            | 81 (63) |         |         |
| IgA            | 17 (13) |         |         |
| IgM            | 23 (18) |         |         |
| Biclonal†      | 8 (6)  |         |         |

Notes: BEEA, Biomarkers of Exposure and Effect in Agriculture study; Ig, immunoglobulin; IQR, interquartile range; MGUS, monoclonal gammopathy of undetermined significance.
*Wilcoxon rank-sum test.
†Chi-square test.
‡Includes two IgG biclonal, three IgG and IgA biclonal, and three IgG and IgM biclonal.

MGUS and evaluated associations with cumulative intensity-weighted lifetime days of pesticide use in the pooled data set using similar statistical methods as for the primary analyses among BEEA participants, with additional adjustment for study group (BEEA, prior AHS study of MGUS) in the pesticide-specific analyses.

Statistical analyses were performed in SAS (version 9.4; SAS Institute Inc.) and Stata (release 15.0; Stata Corporation). All tests were two-sided with α = 0.05.

Results

The median age of participants at BEEA enrollment was 64 y (interquartile range: 58–72 y), and most participants were from Iowa (Table 1). Compared with those without MGUS, the MGUS cases were somewhat older and a higher proportion were from North Carolina.

The age-standardized prevalence of MGUS among BEEA participants was 7.7% (95% CI: 6.3, 9.1%), which was more than twice as high as the prevalence among demographically similar men in Olmsted County and White males of similar age in NHANES (p < 0.001 for both reference populations; Table 2).

Age-specific MGUS prevalence estimates increased with age and were consistently higher among BEEA participants (e.g., from 4.4% among those 30–59 years of age to 18.2% among those ≥80 years of age) relative to general population estimates (50–59 years of age: 0.6% in NHANES and 2.0% in Olmsted County; ≥80 years of age: 6.1% in NHANES and 8.3% in Olmsted County). A similar excess of MGUS was observed among the pooled set of participants from BEEA and the previous study of MGUS in the AHS [age-standardized MGUS prevalence of 7.6% (95% CI: 6.4, 8.8%); Table S1].

We observed statistically significant associations with overall and non-IgM MGUS for intensity-weighted lifetime days of use of several pesticides (Table 3). High intensity-weighted lifetime days of aldrin and dieldrin use was associated with both overall MGUS [OR = 2.42 (95% CI: 1.29, 4.54), p-trend = 0.006] and non-IgM MGUS [OR = 2.39 (95% CI: 1.21, 4.72), p-trend = 0.01] compared with participants who never used aldrin or dieldrin; associations were similar for aldrin use alone. We also observed a positive nonsignificant association with non-IgM MGUS for high intensity-weighted lifetime days of lindane use [OR = 1.92 (95% CI: 0.96, 3.83), p-trend = 0.006]. High use of petroleum oil/distillates was associated with MGUS [OR = 2.34 (95% CI: 1.27, 4.33), p-trend = 0.008]. Low use of diazinon was also associated with MGUS [OR = 2.25 (95% CI: 1.26, 4.02)], but there was no association with high diazinon use and no evidence of an exposure–response trend (p-trend = 0.96). High use of fonofos was inversely associated with MGUS [OR = 0.38 (95% CI: 0.18, 0.80), p-trend = 0.01], although this finding was based on a small number of highly exposed cases (n = 8). Further adjustment for other pesticides associated with MGUS among BEEA participants did not materially change our findings (Table S2); the p-values for exposure–response trends with overall and non-IgM MGUS for aldrin/dieldrin, fonofos, and petroleum oil/distillates remained statistically significant, and ORs for the highest category of use were similar (i.e., differences of ≤10%). For lindane and diazinon, the p-values for exposure–response trends remained nonsignificant, and ORs changed by ≤20%.

Results for intensity-weighted lifetime days of pesticide use were generally similar in the pooled set of AHS participants including those from the earlier MGUS study (Table S3), although for lindane the association between high use and non-IgM MGUS was similar to that observed among BEEA participants but reached statistical significance in pooled analyses [BEEA only: OR = 1.92 (95% CI: 0.96, 3.83), p-trend = 0.06; pooled analysis: OR = 2.02 (95% CI: 1.12, 3.67), p-trend = 0.02]. We also observed associations with ever use of carbon tetrachloride/carbon disulfide [OR = 1.67 (95% CI: 1.04, 2.69)] and chlorothalonil [OR = 1.88 (95% CI: 1.07, 3.31)] in pooled analyses (Table S4).

Table 2. Prevalence of MGUS among male farmers in the BEEA study and demographically similar populations in NHANES and Olmsted County, Minnesota.

| Age group (y) | BEEA Study* | NHANES* | Olmsted County, Minnesota* |
|---------------|-------------|---------|---------------------------|
|               | Prevalence (%) (95% CI) | Prevalence (%) (95% CI) | Prevalence (%) (95% CI) |
| 50–59         | 4.4 (2.6, 6.2) | 0.6 (0.3, 1.1) | 2.0 (1.6, 2.5) |
| 60–69         | 7.3 (5.1, 9.4) | 3.4 (2.3, 4.9) | 3.7 (3.0, 4.4) |
| 70–79         | 10.4 (7.3, 13.4) | 5.2 (3.9, 6.9) | 5.6 (4.5, 6.7) |
| ≥80           | 18.2 (10.2, 26.2) | 6.1 (4.4, 8.4) | 8.3 (6.2, 10.4) |
| Total         | 7.7 (6.3, 9.1) | 2.8 (2.4, 3.2) | 3.8 (3.4, 4.2) |

Notes: AHS, Agricultural Health Study; BEEA, Biomarkers of Exposure and Effect in Agriculture; CI, confidence interval; MGUS, monoclonal gammopathy of undetermined significance; NHANES, National Health and Nutrition Examination Survey.
*Estimated prevalence among participants in the BEEA study, which included male AHS farmers ≥50 years of age with samples collected in 2010–2017 (Hofmann et al. 2015).
†Estimated prevalence among White males ≥50 years of age in NHANES for the years 1988–1994 and 1999–2004 (Landrègne et al. 2014).
‡Estimated prevalence among males ≥50 years of age in the mostly White population of Olmsted County, Minnesota, for the years 1995–2001 (Kyle et al. 2006).
§Age-standardized to the U.S. population of White males ≥50 years of age based on the 2000 U.S. Census population.
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Table 3. Intensity-weighted lifetime days of pesticide use and MGUS among BEEA participants.

| Pesticide                  | Exposure group | n_cases | OR (95% CI)* | n_cases | OR (95% CI)* |
|---------------------------|----------------|---------|--------------|---------|--------------|
| **Organochlorine insecticides** |                |         |              |         |              |
| Aldrin                    | Never          | 88      | 1.00 (Ref)   | 71      | 1.00 (Ref)   |
|                           | ≤ Median       | 10      | 1.47 (0.71, 3.05) | 8     | 1.41 (0.63, 3.14) |
|                           | > Median       | 15      | 2.33 (1.23, 4.40) | 12   | 2.24 (1.12, 4.49) |
|                          | trend = 0.01   |         |              |         |              |
| Aldrin/dieldrin combined   | Never          | 86      | 1.00 (Ref)   | 70      | 1.00 (Ref)   |
|                           | ≤ Median       | 9       | 1.32 (0.62, 2.83) | 7     | 1.23 (0.53, 2.86) |
|                           | > Median       | 16      | 2.42 (1.29, 4.54) | 13   | 2.39 (1.21, 4.72) |
|                          | trend = 0.006  |         |              |         |              |
| Chlor dane                | Never          | 84      | 1.00 (Ref)   | 69      | 1.00 (Ref)   |
|                           | ≤ Median       | 9       | 1.10 (0.53, 2.30) | 8     | 1.19 (0.55, 2.58) |
|                           | > Median       | 9       | 0.94 (0.45, 2.00) | 8     | 1.06 (0.48, 2.33) |
|                          | trend = 0.86   |         |              |         |              |
| DDT                       | Never          | 85      | 1.00 (Ref)   | 69      | 1.00 (Ref)   |
|                           | ≤ Median       | 9       | 0.85 (0.40, 1.80) | 8     | 0.96 (0.43, 2.12) |
|                           | > Median       | 10      | 0.83 (0.39, 1.76) | 8     | 0.83 (0.37, 1.89) |
|                          | trend = 0.66   |         |              |         |              |
| Heptachlor                | Never          | 94      | 1.00 (Ref)   | 75      | 1.00 (Ref)   |
|                           | ≤ Median       | 7       | 1.12 (0.49, 2.57) | 6     | 1.13 (0.46, 2.77) |
|                           | > Median       | 10      | 1.47 (0.71, 3.05) | 9     | 1.65 (0.76, 3.56) |
|                          | trend = 0.20   |         |              |         |              |
| Lindane                   | Never          | 84      | 1.00 (Ref)   | 69      | 1.00 (Ref)   |
|                           | ≤ Median       | 7       | 0.95 (0.42, 2.16) | 6     | 0.95 (0.40, 2.29) |
|                           | > Median       | 12      | 1.70 (0.88, 3.29) | 11    | 1.92 (0.96, 3.83) |
|                          | trend = 0.12   |         |              |         |              |
| **Organophosphate insecticides** |                |         |              |         |              |
| Chloryprifos              | Never          | 59      | 1.00 (Ref)   | 49      | 1.00 (Ref)   |
|                           | Tertile 1      | 20      | 1.03 (0.60, 1.77) | 16    | 0.97 (0.53, 1.75) |
|                           | Tertile 2      | 24      | 1.25 (0.75, 2.07) | 21    | 1.29 (0.75, 2.21) |
|                           | Tertile 3      | 25      | 1.34 (0.81, 2.21) | 19    | 1.19 (0.68, 2.09) |
|                          | trend = 0.49   |         |              |         |              |
| Coumaphos                 | Never          | 111     | 1.00 (Ref)   | 91      | 1.00 (Ref)   |
|                           | ≤ Median       | 9       | 1.27 (0.61, 2.61) | 8     | 1.35 (0.63, 2.89) |
|                           | > Median       | 8       | 1.22 (0.57, 2.60) | 7     | 1.34 (0.60, 3.01) |
|                          | trend = 0.33   |         |              |         |              |
| Diazinon                  | Never          | 73      | 1.00 (Ref)   | 60      | 1.00 (Ref)   |
|                           | ≤ Median       | 17      | 2.25 (1.26, 4.02) | 14    | 2.20 (1.17, 4.13) |
|                           | > Median       | 10      | 1.00 (0.48, 2.10) | 9     | 1.17 (0.54, 2.54) |
|                          | trend = 0.76   |         |              |         |              |
| Dichlorvos                | Never          | 103     | 1.00 (Ref)   | 85      | 1.00 (Ref)   |
|                           | ≤ Median       | 10      | 1.18 (0.59, 2.36) | 10    | 1.38 (0.69, 2.78) |
|                           | > Median       | 10      | 1.70 (0.92, 3.12) | 10    | 1.44 (0.72, 2.90) |
|                          | trend = 0.33   |         |              |         |              |
| Fonofos                   | Never          | 100     | 1.00 (Ref)   | 84      | 1.00 (Ref)   |
|                           | ≤ Median       | 21      | 1.09 (0.65, 1.82) | 15    | 0.85 (0.47, 1.53) |
|                           | > Median       | 8       | 0.38 (0.18, 0.80) | 7     | 0.38 (0.17, 0.85) |
|                          | trend = 0.02   |         |              |         |              |
| Malathion                 | Never          | 26      | 1.00 (Ref)   | 23      | 1.00 (Ref)   |
|                           | Tertile 1      | 17      | 0.78 (0.41, 1.48) | 13    | 0.66 (0.32, 1.34) |
|                           | Tertile 2      | 25      | 1.10 (0.62, 1.97) | 24    | 1.20 (0.66, 2.19) |
|                           | Tertile 3      | 27      | 1.14 (0.64, 2.02) | 22    | 1.04 (0.56, 1.92) |
|                          | trend = 0.65   |         |              |         |              |
| Phorate                   | Never          | 82      | 1.00 (Ref)   | 65      | 1.00 (Ref)   |
|                           | ≤ Median       | 15      | 1.12 (0.61, 2.06) | 12    | 1.07 (0.54, 2.10) |
|                           | > Median       | 15      | 1.02 (0.55, 1.88) | 14    | 1.15 (0.61, 2.19) |
|                          | trend = 0.68   |         |              |         |              |
| Terbufos                  | Never          | 72      | 1.00 (Ref)   | 57      | 1.00 (Ref)   |
|                           | ≤ Median       | 25      | 0.87 (0.53, 1.43) | 21    | 0.88 (0.51, 1.52) |
|                           | > Median       | 30      | 1.01 (0.63, 1.62) | 27    | 1.12 (0.67, 1.85) |
|                          | trend = 0.56   |         |              |         |              |
| Carbamate insecticides    |                |         |              |         |              |
| Carbaryl                  | Never          | 43      | 1.00 (Ref)   | 38      | 1.00 (Ref)   |
|                           | ≤ Median       | 26      | 1.52 (0.90, 2.56) | 18    | 1.22 (0.67, 2.19) |
|                           | > Median       | 22      | 1.11 (0.58, 2.12) | 19    | 1.14 (0.57, 2.27) |
|                          | trend = 0.82   |         |              |         |              |
| Carbofuran                | Never          | 83      | 1.00 (Ref)   | 66      | 1.00 (Ref)   |
|                           | ≤ Median       | 18      | 0.75 (0.44, 1.28) | 15    | 0.76 (0.43, 1.37) |
|                           | > Median       | 28      | 1.15 (0.73, 1.81) | 25    | 1.28 (0.79, 2.08) |
|                          | trend = 0.26   |         |              |         |              |
Table 3. (Continued.)

| Pesticide            | Exposure group | Overall MGUS | Non-IgM MGUS |
|----------------------|----------------|--------------|--------------|
|                      | \( n_{\text{cases}} \) | OR (95% CI)  | \( n_{\text{cases}} \) | OR (95% CI) |
| **Pyrethroid insecticides** |               |              |              |
| Permethrin           |                |              |              |
| Never                | 81             | 1.00 (Ref)   | 66           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 27             | 1.50 (0.93, 2.40) | 22 | 1.42 (0.85, 2.37) |
| >Median              | 20             | 1.13 (0.67, 1.91) | 18 | 1.23 (0.71, 2.14) |
| \( p_{\text{trend}} = 0.76 \) |                |              |              |
| **Herbicides**       |                |              |              |
| 2,4-D                |                |              |              |
| Never                | 18             | 1.00 (Ref)   | 13           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 28             | 1.32 (0.70, 2.48) | 21 | 1.31 (0.63, 2.69) |
| \( >\text{Median} \)  | 27             | 1.36 (0.73, 2.56) | 26 | 1.57 (0.77, 3.19) |
|                      |                |              |              |
| 2,4,5-T              |                |              |              |
| Never                | 86             | 1.00 (Ref)   | 72           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 9              | 0.78 (0.38, 1.63) | 7  | 0.71 (0.31, 1.61) |
| >Median              | 10             | 0.83 (0.41, 1.68) | 7  | 0.70 (0.31, 1.59) |
| \( p_{\text{trend}} = 0.60 \) |                |              |              |
| Alachlor             |                |              |              |
| Never                | 53             | 1.00 (Ref)   | 42           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 27             | 1.08 (0.66, 1.79) | 23 | 1.13 (0.65, 1.95) |
| \( >\text{Median} \)  | 23             | 0.88 (0.52, 1.49) | 18 | 0.85 (0.48, 1.53) |
|                      |                |              |              |
| Atrazine             |                |              |              |
| Never                | 23             | 1.00 (Ref)   | 18           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 29             | 1.02 (0.56, 1.86) | 22 | 0.94 (0.48, 1.85) |
| \( >\text{Median} \)  | 21             | 0.80 (0.41, 1.55) | 19 | 0.89 (0.43, 1.81) |
|                      |                |              |              |
| Butylate             |                |              |              |
| Never                | 74             | 1.00 (Ref)   | 61           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 18             | 1.54 (0.88, 2.70) | 16 | 1.59 (0.88, 2.88) |
| >Median              | 17             | 1.48 (0.83, 2.61) | 13 | 1.32 (0.70, 2.49) |
| \( p_{\text{trend}} = 0.20 \) |                |              |              |
| Chlorimuron ethyl    |                |              |              |
| Never                | 86             | 1.00 (Ref)   | 68           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 15             | 1.02 (0.57, 1.84) | 13 | 1.11 (0.59, 2.08) |
| >Median              | 12             | 0.81 (0.43, 1.53) | 11 | 0.92 (0.48, 1.80) |
| \( p_{\text{trend}} = 0.53 \) |                |              |              |
| Cyanazine            |                |              |              |
| Never                | 64             | 1.00 (Ref)   | 52           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 23             | 1.32 (0.77, 2.26) | 19 | 1.25 (0.70, 2.25) |
| \( >\text{Median} \)  | 24             | 1.35 (0.78, 2.32) | 20 | 1.27 (0.71, 2.29) |
|                      |                |              |              |
| Dicamba              |                |              |              |
| Never                | 50             | 1.00 (Ref)   | 40           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 28             | 1.28 (0.75, 2.20) | 23 | 1.25 (0.69, 2.27) |
| \( >\text{Median} \)  | 29             | 1.39 (0.81, 2.40) | 24 | 1.35 (0.75, 2.43) |
|                      |                |              |              |
| EPTC                 |                |              |              |
| Never                | 107            | 1.00 (Ref)   | 89           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 11             | 1.06 (0.55, 2.06) | 9  | 1.03 (0.50, 2.13) |
| >Median              | 10             | 1.01 (0.51, 1.99) | 7  | 0.84 (0.38, 1.87) |
| \( p_{\text{trend}} = 0.98 \) |                |              |              |
| Glyphosate           |                |              |              |
| Never                | 14             | 1.00 (Ref)   | 9            | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 31             | 1.10 (0.56, 2.14) | 26 | 1.41 (0.64, 3.10) |
| \( >\text{Median} \)  | 22             | 0.81 (0.40, 1.64) | 19 | 1.09 (0.48, 2.47) |
|                      |                |              |              |
| Imazethapyr          |                |              |              |
| Never                | 75             | 1.00 (Ref)   | 60           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 27             | 1.27 (0.77, 2.09) | 23 | 1.31 (0.76, 2.26) |
| >Median              | 27             | 1.40 (0.84, 2.32) | 23 | 1.42 (0.82, 2.47) |
| \( p_{\text{trend}} = 0.23 \) |                |              |              |
| Metolachlor          |                |              |              |
| Never                | 67             | 1.00 (Ref)   | 54           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 20             | 0.91 (0.53, 1.55) | 16 | 0.89 (0.49, 1.60) |
| \( >\text{Median} \)  | 17             | 0.83 (0.47, 1.46) | 14 | 0.83 (0.45, 1.55) |
|                      |                |              |              |
| Metribuzin           |                |              |              |
| Never                | 75             | 1.00 (Ref)   | 61           | 1.00 (Ref)   |
| \( \leq \text{Median} \) | 17             | 0.96 (0.54, 1.69) | 14 | 0.93 (0.50, 1.74) |
| >Median              | 12             | 0.69 (0.36, 1.31) | 10 | 0.69 (0.34, 1.38) |
| \( p_{\text{trend}} = 0.26 \) |                |              |              |
In analyses of the five most common recently used pesticides among BEEA participants (Table 4), recent use of permethrin was associated with both overall MGUS [OR = 1.82 (95% CI: 1.06, 3.12)] and non-IgM MGUS [OR = 2.01 (95% CI: 1.13, 3.56)] compared with those with no recent use. The association with permethrin was stronger among those with both past and recent use compared with never users [overall MGUS: OR = 2.49 (95% CI: 1.32, 4.69); non-IgM MGUS: OR = 2.74 (95% CI: 1.42, 5.30)]. With respect to historical lifetime intensity-weighted use of permethrin, we observed a positive nonsignificant association with overall MGUS for low permethrin use [OR = 1.50 (95% CI: 0.93, 2.40)], but an association with high permethrin use was not apparent [OR = 1.13 (95% CI: 0.67, 1.91)], and there was no evidence of an exposure–response trend ($p_{\text{trend}} = 0.76$). For other pesticides, recent use (assessed separately or in combination with past use) was not associated with MGUS. We observed similar findings after adjusting for use of other pesticides associated with MGUS (Table 4). For each of these five pesticides, there were too few cases with recent use only ($n_{\text{cases}} \leq 6$) to evaluate this group separately. Associations with intensity-weighted lifetime use of these pesticides remained nonstatistically significant in analyses excluding those with recent use only (Table S5).

**Discussion**

This study is, to our knowledge, the largest investigation of the myeloma precursor MGUS in a farming population. An elevated prevalence of MGUS was observed previously in a smaller study of male farmers in the AHS (Landgren et al. 2009a) and among crop and cattle farmers in France (Lecluse et al. 2016). Based on these prior smaller studies, we were motivated to conduct a large screening study that was statistically powered to test for associations between MM precursor disease and specific pesticides. Here, we confirm and expand on the previously reported excess of MGUS among farmers relative to prevalence rates in the general population. For the first time, we identified an association between permethrin and MGUS; exposures to permethrin and several other pesticides may contribute to the elevated risk of MM in farming populations in the United States and other countries (Alavanja et al. 2005; Koutros et al. 2010; Lemarchand et al. 2017; Lerro et al. 2019; Lope et al. 2008; Perrotta et al. 2008).

Permethrin is a broad-spectrum synthetic pyrethroid insecticide that is widely used in agriculture for insect and parasite control in both crop and livestock farming (U.S. EPA 2009). In addition to agricultural applications, exposure to permethrin is common in the general U.S. population (Barr et al. 2010), where it is used in homes and gardens, in mosquito abatement programs, for flea and tick control on dogs, and for medical treatment of lice and scabies, as well as in treated outdoor clothing and battle dress uniforms for military personnel (ATSDR 2003; Kegel et al. 2014; U.S. EPA 2009). Permethrin is classified by the U.S. Environmental Protection Agency as “likely to be carcinogenic to humans” by the oral route of exposure based on evidence from studies in mice (U.S. EPA 2009). Experimental studies have noted evidence of permethrin-induced bone marrow toxicity; studies of oral administration demonstrated an increased number of chromosomal aberrations and increased micronuclei frequency in bone marrow cells from male Wistar rats and female Sprague-

**Table 3. (Continued.)**

| Pesticide | Exposure group | Overall MGUS | Non-IgM MGUS |
|-----------|----------------|--------------|--------------|
|           | $n_{\text{cases}}$ | OR (95% CI)* | $n_{\text{cases}}$ | OR (95% CI)* |
| Paraquat  | Never          | 96           | 1.00 (Ref)   | 81           | 1.00 (Ref)   |
|           | $\leq$Median   | 7            | 0.92 (0.41, 2.08) | 7           | 1.12 (0.50, 2.54) |
|           | $>\text{Median}$ | 7           | 0.84 (0.36, 2.01) | 5           | 0.79 (0.29, 2.13) |
|          | $p_{\text{trend}} = 0.70$ |              | $p_{\text{trend}} = 0.64$ |
| Pendimethalin | Never         | 79           | 1.00 (Ref)   | 66           | 1.00 (Ref)   |
|           | $\leq$Median   | 14           | 0.66 (0.36, 1.19) | 12          | 0.66 (0.35, 1.25) |
|           | $>\text{Median}$ | 16           | 0.78 (0.44, 1.37) | 13          | 0.75 (0.40, 1.39) |
|          | $p_{\text{trend}} = 0.42$ |              | $p_{\text{trend}} = 0.39$ |
| Petroleum oil/distillates | Never       | 50           | 1.00 (Ref)   | 39           | 1.00 (Ref)   |
|           | $\leq$Median   | 11           | 1.51 (0.75, 3.05) | 9           | 1.56 (0.72, 3.37) |
|           | $>\text{Median}$ | 17           | 2.34 (1.27, 4.33) | 14          | 2.39 (1.22, 4.76) |
|          | $p_{\text{trend}} = 0.008$ |              | $p_{\text{trend}} = 0.01$ |
| Trifluralin | Never          | 71           | 1.00 (Ref)   | 57           | 1.00 (Ref)   |
|           | $\leq$Median   | 32           | 1.15 (0.73, 1.79) | 24          | 1.04 (0.63, 1.73) |
|           | $>\text{Median}$ | 24           | 0.84 (0.52, 1.37) | 23          | 0.99 (0.59, 1.65) |
|          | $p_{\text{trend}} = 0.41$ |              | $p_{\text{trend}} = 0.94$ |
| Fungicides | Captain        | Never        | 107          | 1.00 (Ref)   | 87           | 1.00 (Ref)   |
|           | $\leq$Median   | 7            | 1.03 (0.46, 2.31) | 6           | 1.06 (0.43, 2.53) |
|           | $>\text{Median}$ | 11           | 1.41 (0.73, 2.75) | 9           | 1.42 (0.69, 2.93) |
|          | $p_{\text{trend}} = 0.31$ |              | $p_{\text{trend}} = 0.35$ |
|           | Metalaxyl      | Never        | 102          | 1.00 (Ref)   | 84           | 1.00 (Ref)   |
|           | $\leq$Median   | 3            | 0.33 (0.10, 1.06) | 3           | 0.39 (0.12, 1.28) |
|           | $>\text{Median}$ | 7            | 0.65 (0.27, 1.54) | 5           | 0.57 (0.21, 1.58) |
|          | $p_{\text{trend}} = 0.41$ |              | $p_{\text{trend}} = 0.34$ |
|           | Fumigants      | Methyl bromide | Never  | 108 | 1.00 (Ref) | 91 | 1.00 (Ref) |
|           | $\leq$Median | 8            | 0.93 (0.41, 2.14) | 5           | 0.71 (0.26, 1.94) |
|           | $>\text{Median}$ | 13           | 1.27 (0.60, 2.69) | 10          | 1.23 (0.54, 2.84) |
|          | $p_{\text{trend}} = 0.50$ |              | $p_{\text{trend}} = 0.53$ |

Note: Exposure to each pesticide was estimated based on reported use from questionnaires administered at AHS enrollment (1993–1997) and two follow-up interviews (1999–2003, 2005–2010). The number of MGUS cases may not sum to the total (overall MGUS, $n = 129$; non-IgM MGUS, $n = 106$) due to missing information on use of specific pesticides for some participants. AHS, Agricultural Health Study; BEBA, Biomarkers of Exposure and Effect in Agriculture; CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl dipropylthiocarbamate; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; Ref, reference; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

*Adjusted for age at BEBA enrollment and state of residence.
### Pesticide Exposure and MGUS

**Table 4. Recent use of selected pesticides and MGUS among BEEA participants.**

| Pesticide | Overall MGUS | Non-IgM MGUS |
|-----------|--------------|--------------|
|           | Main model\(^a\) | Expanded model\(^b\) | n\(_{\text{cases}}\) | OR (95% CI) | OR (95% CI) | n\(_{\text{cases}}\) | OR (95% CI) | OR (95% CI) |
| Insecticides | | | | | | | | |
| Malathion | | | | | | | | |
| Recent use | No | 109 | 1.00 (Ref) | 1.00 (Ref) | 90 | 1.00 (Ref) | 1.00 (Ref) |
| | Yes | 20 | 1.35 (0.81, 2.27) | 1.30 (0.77, 2.19) | 16 | 1.26 (0.71, 2.22) | 1.19 (0.67, 2.12) |
| Past/recent use | Neither | 24 | 1.00 (Ref) | 1.00 (Ref) | 21 | 1.00 (Ref) | 1.00 (Ref) |
| | Past only | 85 | 0.99 (0.62, 1.60) | 0.85 (0.51, 1.39) | 69 | 0.91 (0.55, 1.52) | 0.76 (0.45, 1.30) |
| | Recent only | 2 | — | — | 2 | — | — |
| | Both | 18 | 1.31 (0.68, 2.53) | 1.10 (0.56, 2.15) | 14 | 1.11 (0.54, 2.28) | 0.89 (0.43, 1.87) |
| Permethrin | | | | | | | | |
| Recent use | No | 111 | 1.00 (Ref) | 1.00 (Ref) | 90 | 1.00 (Ref) | 1.00 (Ref) |
| | Yes | 18 | 1.82 (1.06, 3.12) | 1.83 (1.07, 3.15) | 16 | 2.01 (1.13, 3.56) | 2.05 (1.15, 3.65) |
| Past/recent use | Neither | 77 | 1.00 (Ref) | 1.00 (Ref) | 63 | 1.00 (Ref) | 1.00 (Ref) |
| | Past only | 34 | 1.07 (0.70, 1.66) | 1.04 (0.67, 1.61) | 27 | 1.01 (0.63, 1.63) | 0.98 (0.61, 1.60) |
| | Recent only | 4 | — | — | 3 | — | — |
| | Both | 14 | 2.49 (1.32, 4.69) | 2.41 (1.27, 4.57) | 13 | 2.74 (1.42, 5.30) | 2.67 (1.57, 5.20) |
| Herbicides | | | | | | | | |
| 2,4-D | | | | | | | | |
| Recent use | No | 72 | 1.00 (Ref) | 1.00 (Ref) | 56 | 1.00 (Ref) | 1.00 (Ref) |
| | Yes | 57 | 1.00 (0.68, 1.47) | 0.89 (0.60, 1.33) | 50 | 1.12 (0.73, 1.70) | 0.98 (0.64, 1.51) |
| Past/recent use | Neither | 15 | 1.00 (Ref) | 1.00 (Ref) | 10 | 1.00 (Ref) | 1.00 (Ref) |
| | Past only | 57 | 1.24 (0.68, 2.27) | 1.16 (0.63, 2.14) | 46 | 1.46 (0.71, 2.98) | 1.36 (0.66, 2.81) |
| | Recent only | 3 | — | — | 3 | — | — |
| | Both | 54 | 1.20 (0.64, 2.26) | 1.01 (0.53, 1.93) | 47 | 1.52 (0.73, 3.16) | 1.26 (0.60, 2.66) |
| Atrazine | | | | | | | | |
| Recent use | No | 109 | 1.00 (Ref) | 1.00 (Ref) | 92 | 1.00 (Ref) | 1.00 (Ref) |
| | Yes | 20 | 0.83 (0.49, 1.39) | 0.77 (0.45, 1.29) | 14 | 0.67 (0.37, 1.22) | 0.60 (0.33, 1.10) |
| Past/recent use | Neither | 23 | 1.00 (Ref) | 1.00 (Ref) | 18 | 1.00 (Ref) | 1.00 (Ref) |
| | Past only | 86 | 0.96 (0.57, 1.63) | 0.86 (0.50, 1.48) | 74 | 0.99 (0.56, 1.78) | 0.89 (0.49, 1.62) |
| | Recent only | 0 | — | — | 0 | — | — |
| | Both | 20 | 0.82 (0.41, 1.63) | 0.69 (0.34, 1.39) | 14 | 0.68 (0.31, 1.49) | 0.56 (0.25, 1.24) |
| Glyphosate | | | | | | | | |
| Recent use | No | 63 | 1.00 (Ref) | 1.00 (Ref) | 53 | 1.00 (Ref) | 1.00 (Ref) |
| | Yes | 66 | 1.01 (0.69, 1.49) | 0.92 (0.62, 1.36) | 53 | 0.94 (0.62, 1.44) | 0.85 (0.55, 1.30) |
| Past/recent use | Neither | 8 | 1.00 (Ref) | 1.00 (Ref) | 6 | 1.00 (Ref) | 1.00 (Ref) |
| | Past only | 55 | 1.44 (0.65, 3.15) | 1.25 (0.57, 2.76) | 47 | 1.63 (0.67, 3.97) | 1.41 (0.58, 3.47) |
| | Recent only | 6 | — | — | 3 | — | — |
| | Both | 60 | 1.33 (0.60, 2.93) | 1.07 (0.48, 2.38) | 50 | 1.44 (0.59, 3.50) | 1.14 (0.46, 2.82) |

Note: Analyses were restricted to 5 pesticides (2 insecticides, 3 herbicides) with \( \geq 10 \) MGUS cases reporting use in the last 12 months prior to sample collection. —, no data (too few exposed MGUS cases); AHS, Agricultural Health Study; BEEA, Biomarkers of Exposure and Effect in Agriculture; CI, confidence interval; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; Ref, reference; \( 2,4\)-D, \( 2,4\)-dichlorophenoxyacetic acid.

\(^a\)Adjusted for age at BEEA enrollment and state of residence.

\(^b\)Adjusted for age at BEEA enrollment; state of residence; lifetime use of aldrin/dieldrin, petroleum oil/distillates, and fonofos; and recent use of permethrin.

\(^c\)Past use was defined as reported occupational use in the last 12 months prior to sample collection.

\(^d\)Recent use of each pesticide was defined as occupational use in the last 12 months as reported on the questionnaire administered at the time of BEEA enrollment/sample collection.

\(^e\)Main model: no data (too few exposed MGUS cases; AHS, Agricultural Health Study; BEEA, Biomarkers of Exposure and Effect in Agriculture; CI, confidence interval; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; Ref, reference; 2,4-D, 2,4-dichlorophenoxyacetic acid).

\(^f\)Expanded model: no data (too few exposed MGUS cases; AHS, Agricultural Health Study; BEEA, Biomarkers of Exposure and Effect in Agriculture; CI, confidence interval; MGUS, monoclonal gammopathy of undetermined significance; OR, odds ratio; Ref, reference; 2,4-D, 2,4-dichlorophenoxyacetic acid).

Dawley rats, respectively (Hoellinger et al. 1987; Institóris et al. 1999). More recently, an in vitro study of cultured peripheral blood mononuclear cells exposed to low levels of permethrin reported structural aberrations and increased DNA damage in IGH and KMT2A genes (Navarrete-Meneses et al. 2018), both of which are commonly mutated in malignant plasma cells (Kim et al. 2014; Landry et al. 2013). Notably, in the present study, we found that the risk of MGUS more than doubled among pesticide applicators with continued use of permethrin over their working lifetime (based on reported historical use from the previous AHS enrollment or follow-up questionnaires in combination with reported recent use within the last 12 months at BEEA enrollment) compared with never users (defined as no reported permethrin use on all AHS and BEEA questionnaires).

Several factors might explain why we observed associations with MGUS for recent and continued permethrin use but not with historical use, including increased susceptibility to permethrin exposure at older vs. younger ages and potentially greater nondifferential classification of past permethrin exposure (that could have occurred years earlier) compared with more recent exposure. Regarding the latter point, we note that the AHS enrollment questionnaire (which accounts for most past use) covered a
longer period of time (ranging from ≤1 to ≥30 y) and considered average use over that time, whereas the BEEA interview ascertained use during a shorter and more recent time period (the last 12 months), which may have facilitated better recall of recent use compared with that of past use.

In the AHS, exposure to permethrin has been consistently associated with an increased risk of MM among pesticide applicators, with a significant exposure–response trend (Alavanja et al. 2014; Rusiecki et al. 2009). Furthermore, in a longitudinal study among a subset of BEEA participants with serial sample collections timed specifically in relation to permethrin exposure (Shearer et al. 2019), we observed early subclinical alterations in several hematologic parameters (e.g., decreased red blood cell counts, increased immature granulocytes) in samples collected the day after permethrin use relative to off-season levels, which may be indicative of disrupted hematopoiesis. These findings, taken together with the results of the present study demonstrating an association with MGUS for recent use, especially in combination with past use, provide consistent evidence supporting a link between permethrin and MM development.

We also observed statistically significant associations with MGUS for high lifetime use of the organochlorine insecticides aldrin and dieldrin as well as a positive nonsignificant association with high lifetime use of lindane (gamma-hexachlorocyclohexane). The International Agency for Research on Cancer (IARC) has classified lindane as a Group 1 carcinogen (“carcinogenic to humans”) based on sufficient evidence in humans for non-Hodgkin lymphoma (Loomis et al. 2015), and dieldrin (and aldrin metabolized to dieldrin) is classified as a Group 2A carcinogen (“probably carcinogenic to humans”) with limited or inadequate evidence in humans (Guyton et al. 2016). In the prior AHS investigation (Langdren et al. 2009a), ever use of dieldrin was associated with MGUS, and positive nonsignificant associations were observed for aldrin and lindane. In a previous investigation of lymphoid malignancies (including MM) among pesticide applicators in the AHS (Alavanja et al. 2014), ever use of aldrin was associated with a nonstatistically significant elevated risk of MM, and high lifetime days of lindane use was associated with a significantly increased risk of lymphoid malignancies overall, although there were too few exposed cases to evaluate MM separately (Alavanja et al. 2014). Beyond the AHS, the relationship between occupational or environmental exposure to organochlorine insecticides and MM has been investigated in recent case–control studies (Presutti et al. 2016; Weber et al. 2018). Although MM was associated with several organochlorines, including beta-hexachlorocyclohexane, which is structurally similar to lindane, those studies had limited data for the specific organochlorines associated with MGUS in our investigation.

High intensity-weighted lifetime days of use of petroleum oil/distillates as an herbicide was associated with MGUS. The vast majority (>90%) of those reporting use of petroleum oil/distillates indicated that they had used these chemicals during or before the 1980s; during this time period, petroleum-derived products often contained benzene as a trace impurity or residual component (Kopstein 2006; Williams et al. 2008). If the products used contained small concentrations of benzene, it is possible that farmers may have been exposed to volatilized benzene during applications. A growing body of evidence has linked benzene exposure to an increased risk of MM (De Roos et al. 2018; Infante 2006; Loomis et al. 2017; Purdue et al. 2018; Vlaanderen et al. 2011). However, given the heterogeneous composition of petroleum oils and distillates and their various uses in agriculture (Monaco et al. 2002), and the lack of detailed information about use of these products based on available questionnaire data, these findings for MGUS should be interpreted cautiously.

An inverse association with MGUS was observed for those with high intensity-weighted lifetime days of fonofos use. Fonofos, an organophosphate insecticide, was not associated with MM or other lymphoid malignancies in the most recent analysis among pesticide applicators in the AHS (Alavanja et al. 2014), and we are unaware of any other studies linking fonofos use to MM. Given the small number of fonofos-exposed MGUS cases in our investigation (n = 8 in the highest category) and the lack of prior evidence supporting this finding, the interpretation of these results is unclear.

This study had several important strengths. We used detailed information that was collected prospectively in prior AHS interviews to characterize cumulative lifetime exposure to specific pesticides. Although based on self-reported information, farmers are generally knowledgeable about their use of pesticides, and reported information on pesticide use among AHS participants has been shown to be reliable (Blair et al. 2002; Hoppin et al. 2002). Furthermore, exposure intensity-weighting scores have correlated well with urinary measures of exposure (Coble et al. 2011; Thomas et al. 2010). We were also able to conduct analyses of several pesticides using information about more recent use (in the last 12 months prior to BEEA enrollment). All exposure information was collected prior to phlebotomy, and, as such, recall bias is not a concern and any exposure misclassification is non-differential with respect to MGUS. In addition, given that this is the largest investigation of MGUS among farmers, we were able to evaluate associations with many different pesticides, including some that have not been assessed in relation to MM in the AHS, and to adjust for exposure to other pesticides. The assays characterizing MGUS were conducted in a blinded fashion in a laboratory with considerable expertise in conducting studies of MGUS (Langdren et al. 2018), and demonstrated high reproducibility.

Several limitations should also be noted. We assessed MGUS prevalence at BEEA enrollment, but as in other population-based studies of MGUS, the timing of onset of this largely asymptomatic precursor is unknown. Although we did not have an internal reference group of nonfarmers, use of specific pesticides varied widely among participants, allowing us to evaluate MGUS in relation to individual chemicals. Furthermore, we were able to compare the MGUS prevalence among farmers in our study with that of demographically similar men in Minnesota and a nationally representative sample in NHANES, and we observed consistent evidence of an elevated prevalence of MGUS in our study compared with both general nonfarming populations. Our study was restricted to individuals ≥50 years of age for comparison with these populations and in consideration of the low prevalence of MGUS among younger individuals (Langdren et al. 2017). Given that this investigation was conducted among male farmers, it remains unclear whether these findings are generalizable to other populations. However, by focusing on a population with high occupational pesticide exposures, our study provides insights into the etiology of MM and the role of specific pesticides in the development of this malignancy that warrant further investigation in other groups (in particular among female farmers or spouses living on the farm, as well as African Americans and other racial/ethnic minority groups). Additional studies are also needed to further characterize the biologic plausibility and mechanisms of action through which specific pesticides may influence MM development, thereby informing assessments of carcinogenicity by public health and regulatory bodies. Finally, we note that the small numbers of exposed cases for some pesticides limited our ability to evaluate associations with MGUS for those chemicals, and future studies following up on these findings in larger samples would be informative.

In summary, in this prospective investigation with detailed information on lifetime pesticide use, we confirmed the previously
observed excess of MGUS among male farmers and expanded our knowledge on this topic by identifying associations with MGUS for several pesticides, including the organochlorine insecticides aldrin and dieldrin, petroleum oil/distillates, and permethrin, a widely used pyrethroid insecticide that has previously been associated with an increased risk of MM in the AHS. Our findings provide important insights regarding exposures to specific pesticides that may contribute to the excess of MM among farmers. The magnitude of exposure to these pesticides in our study population is likely to be substantially higher than in the general population, and whether exposures at lower levels may influence risk of MM or its precursor remains unknown. However, given the continued widespread residential and other use of permethrin and environmental exposure to organochlorine insecticides (including aldrin, dieldrin, and lindane) due to legacy contamination and continued use in some countries, associations with these pesticides (even if more modest than those observed in our study) could have important public health implications for exposed individuals in the general population.

Acknowledgments

We thank A. Miller, K. Torres, S. Balogh, H. Singh, and M. Dunn (Westat, Rockville, Maryland) and D. Podaril, D. Lande, and J. Hamilton (University of Iowa) for study coordination, data management, and field research efforts. We also thank Anne Taylor and Peter Hui (Information Management Services, Rockville, Maryland) for data management and analytic support. The authors gratefully acknowledge the ongoing participation of the Agricultural Health Study participants that made this work possible.

This work was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute (Z01 CP 011019) and the National Institute of Environmental Health Sciences (Z01 ES 049030), by the U.S. Environmental Protection Agency through an interagency agreement (XCP13001-001-0003), by a memorial Sloan Kettering Core Grant (P30 CA008748), and by the Perelman Family Foundation in collaboration with the Multiple Myeloma Research Foundation (MMRF).

References

Alavanja MCR, Hofmann JN, Beane Freeman LE, Lynch CF, Andretti G, Thomas KW, Sandler DP, et al. 2015. The Biomarkers of Exposure and Effect in Agriculture (BEEA) study: rationale, design, methods, and participant characteristics. J Toxicol Environ Health A 78(21-22):1389–1347, PMID: 26655555, https://doi.org/10.1080/03603019.2015.1016267.

Hoppin JA, Yauce F, Dossegem M, Sandler DP. 2002. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Epidemiol 12(5):313–318, PMID: 12198579, https://doi.org/10.1093/aje/70.3.1279.

Infante FF. 2006. Benzo[a]pyrene exposure and multiple myeloma: a detailed meta-analysis of benzo[a]pyrene cohort studies. Ann NY Acad Sci 1076:90–109, PMID: 17119155, https://doi.org/10.1196/annals.1371.081.

Institóris L, Underger U, Siroki O, Nehéz M, Dési I. 1999. Comparison of detection sensitivity of immuno- and genotoxicological effects of subacute cypermethrin and permethrin exposure in rats. Toxicology 137(1):47–55, PMID: 10513999, https://doi.org/10.1016/S0300-483X(99)00001-5.

Kegel P, Letzel S, Rossbach B. 2014. Biomonitoring in wearers of permethrin impregnated battle dress uniforms in Afghanistan and Germany. Occup Environ Med 71(12):112–117, PMID: 24343973, https://doi.org/10.1136/oemed-2012-101276.

Kim GY, Gabrea A, Demchenko YN, Bergsagel L, Roschke AV, Kheil WM. 2014. Complex IGH rearrangements in multiple myeloma: frequent detection discrepancies among three different probe sets. Genes Chromosomes Cancer 53(6):467–474, PMID: 24585545, https://doi.org/10.1002/gcc.22158.

Kopstein M. 2006. Potential uses of pesticide chemicals in pest control can result in significant benzo[a]pyrene exposures: NSDDS must list benzo[a]pyrene as an ingredient. J Occup Environ Hyg 3(1):81–85, PMID: 16482972, https://doi.org/10.1080/15459620500430508.

Koutros S, Alavanja MCR, Lubin JH, Sandler DP, Hoppin JA, Lynch CF, et al. 2010. An update of cancer incidence in the Agricultural Health Study. J Occup Environ Med 52(11):1089–1105, PMID: 21063187, https://doi.org/10.1097/JOM.0b013e31817d6616.

Kyle RA, Larson DR, Therneau TM, Dispensieri A, Kumar S, Cerhan JR, et al. 2018. Long-term follow-up of monoclonal gammopathy of undetermined significance. N Engl J Med 378(3):241–249, PMID: 28342381, https://doi.org/10.1056/NEJMoa1709974.

Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. 2006. Prevalence of monoclonal gammopathy of undetermined significance. N Engl J Med 354(13):1362–1369, PMID: 16571879, https://doi.org/10.1056/NEJMoa054494.

Landgren O, Graubdal BJ, Katzmann JA, Kyle RA, Ahmadizadeh I, Clark R, et al. 2017. Racial disparities in the prevalence of monoclonal gammopathies: a population-based study of 12,482 persons from the National Health and Nutrition Examination Survey. Leukemia 28(7):1537–1542, PMID: 24441287, https://doi.org/10.1038/leu.2014.34.

Landgren O, Graubdal BJ, Kumar S, Kyle RA, Katzmann JA, Murata K, et al. 2017. Prevalence of myeloma precursor state monoclonal gammopathy of undetermined significance in 12372 individuals 10–49 years old: a population-based study from the National Health and Nutrition Examination Survey. Blood Cancer J 7(10):e618, PMID: 29053158, https://doi.org/10.1038/bcj.2017.97.

Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, et al. 2009a. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. Blood 113(25):6386–6394, PMID: 19397605, https://doi.org/10.1182/blood-2008-02-153711.

Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. 2009b. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood 113(22):5412–5417, PMID: 19179464, https://doi.org/10.1182/blood-2008-12-194241.

Landgren O, Shim YK, Michalek J, Costello R, Burton D, Ketchum N, et al. 2015. Agent exposure range and monoclonal gammopathy of undetermined significance: an Operation Ranch Hand veteran cohort study. JAMA Oncol 1(8):1061–1068, PMID: 26335650, https://doi.org/10.1001/jamaoncol.2015.25938.

Landgren O, Zeig-Owens R, Giricz O, Goldfarb D, Murata K, Thoren K, et al. 2018. Multiple myeloma and its precursor disease among firefighters exposed to the World Trade Center disaster. JAMA Oncol 4(6):821–827, PMID: 29710195, https://doi.org/10.1001/jamaoncol.2018.0509.

Landry C, Londono D, Deulin LG, Lasansky A, Indvall N, Hassoun H, et al. 2013. Multiple copies of MLL is the most commonly detected cytogenetic

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abnormality in newly diagnosed multiple myeloma and may modify disease risk. Blood 122(21):1910, https://doi.org/10.1182/blood.V122.21.1910.1910.
Lacelle Y, Comby E, Mariotte D, Tual S, Le Mauff B, Lebailly P, et al. 2016. Prevalence of monoclonal gammapathy of undetermined significance (MGUS) among farmers involved in open field farming and/or cattle breeding in France. Leuk Lymphoma 57(7):1727–1730, PMID: 2668968, https://doi.org/10.3109/10428194.2015.1112277.
Lemarchand C, Tual S, Levêque-Morlais N, Perrier S, Belot A, Velten M, et al. 2017. Cancer incidence in the AGRICAN cohort study (2005–2011). Cancer Epidemiol 49:175–185, PMID: 28790652, https://doi.org/10.1016/j.canep.2017.06.003.
Lerro CC, Koutros S, Andreotti G, Sandler DP, Lynch CF, Louis LM, et al. 2019. Permethrin-exposed pesticide applicators in the Biomarkers of Exposure and Effect in Agriculture study. Occup Environ Med 76(12):891–896, PMID: 30902255, https://doi.org/10.1136/oemed-2018-105559.
Shearer JJ, Beane Freeman LE, Liu D, Andreotti G, Hamilton J, Happel J, et al. 2019. Longitudinal investigation of haematological alterations among permethrin-exposed pesticide applicators in the Biomarkers of Exposure and Effect in Agriculture study. Occup Environ Med 76(7):467–470, PMID: 30902255, https://doi.org/10.1136/oemed-2018-105559.
Thomas KW, Dosemeci M, Coble JB, Hoppin JA, Sheldon LS, Chapa G, et al. 2010. Assessment of a pesticide exposure intensity algorithm in the Agricultural Health Study. J Expo Sci Environ Epidemiol 20(6):559–569, PMID: 20629954, https://doi.org/10.1002/jes.2009.54.
Tual S, Bussan A, Boulanger M, Renier M, Piel C, Poucetieuc C, et al. 2019. Occupational exposure to pesticides and multiple myeloma in the AGRICAN cohort. Cancer Causes Control 30(11):1243–1250, PMID: 31535265, https://doi.org/10.1007/s10552-019-01230-x.
U.S. Census Bureau. 2001. Population by age, sex, race, and Hispanic or Latino origin for the United States: 2000. Report no. PHC-T-9. https://www.census.gov/data/tables/2000/dec/phc-t-09.html [accessed 20 December 2020].
U.S. EPA (U.S. Environmental Protection Agency). 2009. Permethrin facts. https://www3.epa.gov/pesticides/chem_search/reg_actions/reregistration/fs_PC-109701_1-Aug-09.pdf [accessed 20 December 2020].
Vlaanderen J, Lan Q, Kromhout H, Rothman N, Vermeulen R. 2011. Occupational benzene exposure and the risk of lymphoma subtypes: a meta-analysis of cohort studies incorporating three study quality dimensions. Environ Health Perspect 119(2):159–167, PMID: 20880796, https://doi.org/10.1289/ehp.1002318.
Weber L, Song K, Boyle T, Gaudreau É, Lai A, Sutherland HJ, et al. 2018. Organochlorine levels in plasma and risk of multiple myeloma. J Occup Environ Med 60(10):911–916, PMID: 30288832, https://doi.org/10.1097/JOM.0000000000001387.
Williams FRD, Panico JM, Unice K, Brown JL, Paustenbach DJ. 2008. Occupational exposures associated with petroleum-derived products containing trace levels of benzene. J Occup Environ Med 50(9):565–574, PMID: 18915290, https://doi.org/10.1097/JOM.0b013e3181545620802282110.