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Twenty-Three Years of Hypersensitivity Pneumonitis Mortality Surveillance in the United States

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Background *There are few population-based studies addressing hypersensitivity pneumonitis (HP) in the United States. The National Institute for Occupational Safety and Health (NIOSH) has nationally comprehensive longitudinal mortality data that can contribute to a better understanding of the epidemiology of HP.*

Methods *The National Center for Health Statistics multiple cause-of-death data were analyzed for the period 1980–2002. Annual death rate was age-adjusted to the 2000 U.S. standard population. Death rate time-trends were calculated using a linear regression model and geographic distribution of death rates were mapped by state and county. Proportionate mortality ratios (PMRs) by usual industry and occupation adjusted for age, sex, and race, were based on data from 26 states reporting industry and occupation during 1985–1999.*

Results *Overall age-adjusted death rates increased significantly ($P < 0.0001$) between 1980 and 2002, from 0.09 to 0.29 per million. Wisconsin had the highest rate at 1.04 per million. Among industries, PMR for HP was significantly high for agricultural production, livestock (PMR, 19.3; 95% CI, 14.0–25.9) and agricultural production, crops (PMR, 4.3; 95% CI, 3.0–6.0). Among occupations, PMR for HP was significantly elevated for farmers, except horticulture (PMR, 8.1; 95% CI, 6.4–10.2).*

Conclusions *These findings indicate that agricultural industries are closely associated with HP mortality and preventive strategies are needed to protect workers in these industries.* Am. J. Ind. Med. 49:997–1004, 2006. *Published 2006 Wiley-Liss, Inc.*†

KEY WORDS: hypersensitivity pneumonitis; death rate; industry; occupation; agriculture

INTRODUCTION

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an interstitial lung disease caused by inhalation of a variety of agents that are usually organic and antigenic [Schuyler, 1988; Mohr, 2004; Fink et al., 2005]. Mortality rates from HP vary from 1 to 29%, depending on several factors, such as type of exposure and personal susceptibility [Perez-Padilla et al., 1993; Kokkarinen et al., 1994]. The presence of pulmonary fibrosis is an important predictor of HP mortality [Vourlekis et al., 2004].

A broad range of occupations in agricultural, industrial, and office settings have been associated with the risk of HP [Baur, 1995; Alvarez-Fernandez et al., 1998; Calvert et al., 1999; Selman, 2003], and more than 200 different agents have been identified with the development of the disease [Mohr, 2004]. These include plant products, animal products,

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

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aerosolized microorganisms, and chemicals. New etiologies of HP continue to be reported as changing agricultural and industrial practices lead to new types of antigenic exposures. Long-standing but unidentified exposures can also be associated with the disease. For example, HP has been recognized in machinists exposed to aerosolized metal working fluids that are contaminated with microorganisms [Kreiss and Cox-Ganser, 1997]. Although many individuals may be at risk for exposure in their occupational, domestic or recreational environments because of the large number of causative agents for HP, only 5–15% of the individuals in these settings will develop the disease [Selman, 2003].

The National Institute for Occupational Safety and Health (NIOSH) has nationally comprehensive longitudinal mortality data that can contribute to a better understanding of the epidemiology of HP [U.S. Department of Health and Human Services, 2003]. This study provides the demographics and geographic distribution of HP deaths, and also presents the temporal trends in HP death rates for the past 23 years (1980–2002). The results also provide information on the industry and occupational distribution of HP deaths (1985–1999) for selected states for which usual occupation and industry data were available.

METHODS

HP mortality data were obtained from the National Center for Health Statistics (NCHS) multiple cause-of-death data files for the period 1980–2002, for U.S. residents aged $\geq$15 years. Cases with any mention of the Ninth International Classification of Disease (ICD-9), code 495 (extrinsic allergic alveolitis) [U.S. Department of Health and Human Services, 1988] for 1980–1998 and ICD-10 code J67 (HP due to organic dust) [World Health Organization, 1992] for 1999–2002 listed on the entity axis[1] were included in this study [National Center for Health Statistics, 1999].

Age-adjusted death rates per million were calculated based on the 2000 U.S. standard population using SAS software version 8.2 (SAS Institute, Cary, NC). A Chi-square test was performed to evaluate the variability among state death rates. A simple linear regression model (with years, 1980–2002, coded from 0 to 23, respectively), was used to plot the overall trend in rates through 2002. For the geographic distribution of death rates, age-adjusted death rates were mapped for counties with five or more HP deaths using MapInfo Professional software version 7.5 software (MapInfo Corp., Troy, NY).

The proportionate mortality ratio (PMR) adjusted for age, sex, and race was computed by industry and occupation. The data used for the PMR analyses were a subset of the 1985–1999 NCHS multiple cause-of-death files for which the information on usual occupation and industry was available and include data from 26 states (Alaska, Colorado, Georgia, Hawaii, Idaho, Indiana, Kansas, Kentucky, Maine, Missouri, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, North Carolina, Ohio, Oklahoma, Rhode Island, South Carolina, Tennessee, Utah, Vermont, Washington, West Virginia, and Wisconsin). The PMR was defined as the observed number of deaths with the condition of interest in a specified Bureau of Census Industry Code (CIC) or Census Occupation Code (COC) [U.S. Department of Commerce, Economic and Statistics Administration, 1992], divided by the expected number of deaths with that condition. The expected number of deaths was calculated using the total number of deaths in the industry/occupation of interest multiplied by a proportion defined as the number of cause-specific deaths for the condition of interest in all industries/occupations, divided by the total number of deaths in all industries and occupations. In this study, only statistically significant PMRs (i.e., those with a lower 95% confidence limit exceeding 1.0) for those industries/occupations with five or more decedents with HP are reported.

[1] The entity axis preserves diagnosis detail for all listed conditions on the death certificate.

RESULTS

The total number of deaths from HP identified for the years 1980–2002 was 814; 557 (68.4%) were males and 781 (96.0%) were whites. The age-adjusted death rate was 0.33 per million for males compared to 0.10 per million for females; by race, the death rates for white, black, and other races were 0.20, 0.07, and 0.05 per million, respectively (Table Ia). Age-specific death rates increased with age: 0.01 per million for age group 15–24 compared to 0.80 for age group 65 and older (Table Ib).

HP due to unspecified allergic alveolitis and pneumonitis (ICD-9 code 495.9) and unspecified organic dusts (ICD-10 code J67.9) accounted for 55.5% (n = 452) of all HP deaths, while farmer's lung (ICD-9 code 495.0 and ICD-10 code J67.0) was reported in 37.3% (n = 304) (Table II). Together, all other sub-classifications of HP accounted for less than 8% of the total HP deaths.

The 10 states with the highest age-adjusted death rates from HP are demonstrated in Table III. These states account for 57% of all farmers' lung deaths, but only 14% of unspecified HP deaths. Most of these 10 states are clustered in the north-central region of the United States. The distribution of the number of farmer's lung deaths among these states compared to the number of all other sub-classifications of HP varied significantly (Chi-square = 33.45; $P = 0.0001$). Wisconsin was the state with the highest percentage of farmers' lung deaths (81.9%), which was twice that of the U.S. as a whole, and compared to 16.7% in Utah. HP due to

TABLE I. Demographic Characteristics of Decedents With Hypersensitivity Pneumonitis, (a) Age-Adjusted Death Rate (Per Million Per Year) by Sex and Race, and (b) Age-Specific Death Rate (Per Million Per Year), U.S. Residents Aged ≥15 Years, 1980–2002

(a) Demographics	No.	%	Age-adjusted rate/million
Sex			
Male	557	68.4	0.33
Female	257	31.6	0.10
Race			
White	781	96.0	0.20
Black	28	3.4	0.07
Other	5	0.6	0.05
Total	814	100.0	0.19
(b) Age group (years)	**No.**	**%**	**Age-specific rate/million**
15–24	7	0.9	0.01
25–34	19	2.3	0.02
35–44	23	2.8	0.03
45–54	69	8.5	0.12
55–64	108	13.3	0.22
≥65	588	72.2	0.80

unspecified organic dust accounted for 66.7% in Idaho, compared to 8.3% in South Dakota. Age-adjusted HP death rates for counties with five or more deaths (Fig. 2) were widely distributed among counties in Wisconsin, Connecticut, Utah, California, Washington, Missouri, Michigan, Pennsylvania, Illinois, and Florida. Three counties (Vernon, Jefferson, and Dane) in Wisconsin accounted for the highest age-adjusted county death rates: 10.4, 4.6, and 1.2 per million, respectively. Using a simple linear regression analysis, we observed that annual age-adjusted HP death rates increased ($r^2 = 0.59$; $P<0.001$; slope = 0.007) nationwide from 0.09 per million in 1980 to 0.29 per million in 2002 (Fig. 1).

Among industries, significantly elevated PMRs for HP occurred in *agricultural production, livestock* (PMR, 19.3; 95% CI, 14.0–25.9) and *agricultural production, crops* (PMR, 4.3; 95% CI, 3.0–6.0). Among occupations, *farmers, except horticulture* (PMR, 8.1; 95% CI, 6.4–10.2) was the sole occupation with a PMR higher than 1.0 in the states that reported industry and occupation data (Table IV).

DISCUSSION

There were only minor fluctuations in overall employment in the combined agricultural, forestry, fishing, and hunting industries between 1980 and 1999 and sharp declines in 2000 and 2001 [U.S. Department of Labor, 2005]. Therefore, there must be factors other than employment patterns that are driving the increasing trend in national HP death rates, which we observed in the period of our study.

One possible explanation for the increase in reported HP mortality is the evolution of diagnostic technology during the last 20 years, which may have influenced the recognition of this disease. Improved diagnostic techniques include high-resolution computed tomography (HRCT), bronchoalveolar lavage, and transbronchial lung biopsy [Richerson et al., 1989; Akira et al., 1992; Lynch et al., 1992; Schuyler et al., 1997; Selman, 2003].

TABLE II. Number and Percentage of Hypersensitivity Pneumonitis (HP) Deaths by International Classification of Disease (ICD) Sub-Classification, U.S. Residents Aged ≥15 years, 1980–2002

Sub-classification (code)			
ICD-9 (1980–1998)	**ICD-10 (1999–2002)**	**No.**	**%**
Farmers' lung (495.0)	Farmer's lung (J67.0)	304	37.3
Bagassosis (495.1)	Bagassosis (J67.1)	7	0.9
Bird fanciers' lung (495.2)	Bird fancier's lung (J67.2)	36	4.4
Suberosis (495.3)	Suberosis (J67.3)	0	0.0
Malt workers' lung (495.4)	Maltworker's lung (J67.4)	0	0.0
Mushroom workers' lung (495.5)	Mushroom worker's lung (J67.5)	1	0.1
Maple-bark strippers' lung (495.6)	Maple-bark stripper's lung (J67.6)	1	0.1
"Ventilation" pneumonitis (495.7)	Air-conditioner and humidifier lung (J67.7)	10	1.2
Other specified allergic alveolitis and pneumonitis (495.8)	HP due to other organic dusts (J67.8)	17	2.1
Unspecified allergic alveolitis and pneumonitis (495.9)	HP due to unspecified organic dusts (J67.9)	452	55.5
Total		814	101.6

The sum of individual sub-classification deaths and percents are greater than the total number of deaths and percents because 14 decedents have more than one sub-classification listed on their death certificates.

TABLE III. The 10 States With Highest Age-Adjusted Death Rates (Per Million Per Year) of Hypersensitivity Pneumonitis (HP) and Numbers of Deaths With Farmer's Lung (ICD-9 Code 495.0 and ICD-10 Code J67.0) and Unspecified HP (ICD-9 Code 495.9 and ICD-10 Code J67.9), U.S. Residents Aged ≥15 Years, 1980–2002

	Farmer's lung		Unspecified HP		Total HP deaths		
State	No.	%[a]	No.	%[a]	No.	%	Rate
Wisconsin	77	81.9	14	14.9	94	11.5	1.04
Wyoming	4	66.7	2	33.3	6	0.7	0.93
Vermont	6	75.0	2	25.0	8	1.0	0.89
South Dakota	10	83.3	1	8.3	12	1.5	0.86
Idaho	4	33.3	8	66.7	12	1.5	0.69
Iowa	25	69.4	10	27.8	36	4.4	0.64
Minnesota	32	72.7	11	25.0	44	5.4	0.58
Utah	2	16.7	8	66.7	12	1.5	0.50
North Dakota	3	50.0	3	50.0	6	0.7	0.48
Nebraska	9	75.0	3	15.0	12	1.5	0.40
All States	304	37.3	452	55.5	814	100.0	0.19

A total of 52 deaths were recorded in all other sub-classifications of HP.
[a]Percentages in farmer's lung and unspecified HP are based on the total number of HP deaths in each state.

HRCT was introduced in the late 1980s [Mayo et al., 1987] and is constantly evolving. The sensitivity of HRCT for detection of HP is significantly better than that of plain radiographs [Akira et al., 1992; Selman, 2003]. Lynch et al. [1992] reported that the sensitivity of HRCT for the detection of HP in a population-based study was 45%, whereas Fink et al. [2005] found that up to 87% of patients with HP may have a normal plain chest radiograph. Although radiological findings in patients with HP are frequently nonspecific, characteristic patterns may allow the radiologist to discern the correct diagnosis [Matar et al., 2000]. Despite the evidence that HRCT improves diagnostic capability, it is impossible to estimate to what extent its introduction impacted reported death rates. The fact that the trend in Figure 1 did not appear to change in the late 1980s suggests that other factors are more likely to account for the rising death rates from 1980 to 2002.

Another possible underlying factor in the increased trend of HP deaths over time could be decreased smoking in the U.S. The smoking prevalence in the U.S. decreased from 33.2% in 1980 to 22.5% in 2002 among U.S. adults [Husten et al., 2004]. Considerable evidence suggests that smoking inhibits the development of HP. A number of studies have reported that HP is less prevalent in smokers than in nonsmokers [Warren, 1977; Gump et al., 1979; Gruchow et al., 1981; Cormier et al., 1988; Depierre et al., 1988]; in one of these, 95% of HP cases occurred in nonsmokers [Cormier et al., 1988]. A study of farmers in Wisconsin reported that the prevalence of serum precipitating antibodies specific for *Saccharopolyspora rectivirgula* (antigen of farmer's lung) [Schuyler et al., 1997] was eight times higher among farmers who never smoked and the prevalence of farmer's lung disease was six cases per 1,000 farmers among ''never

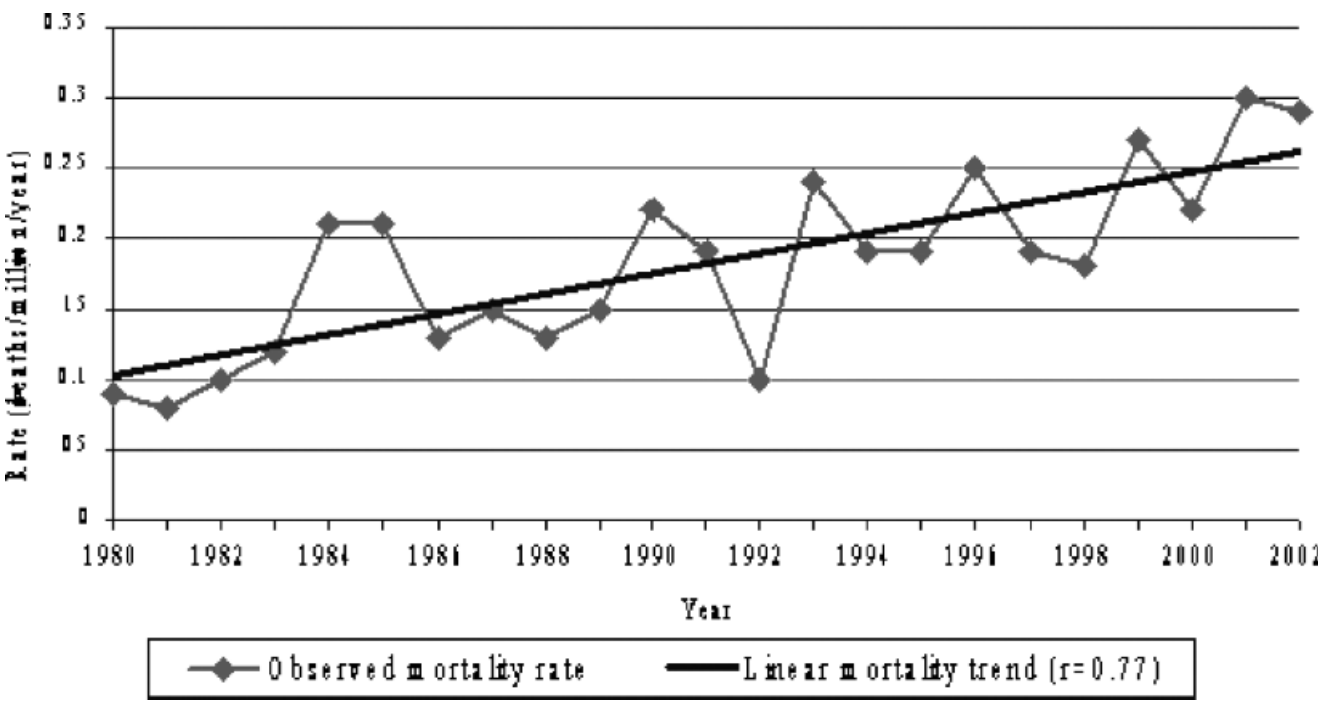

FIGURE 1. Age-adjusted hypersensitivity pneumonitis death rate (per million) by year, U.S. residents aged ≥15 years, 1980–2002.

TABLE IV. Significantly Elevated Proportionate Mortality Ratio (PMR) and 95% Confidence Intervals (CI) For Hypersensitivity Pneumonitis by Industry and Occupation, Selected States and Years, U.S. Residents Aged ≥15 Years, 1985–1999

U.S. Census Bureau Classification (code)	No.	PMR	95% CI
Industry			
Agricultural production, livestock (011)	44	19.3	14.0–25.9
Agricultural production, crops (010)	34	4.3	3.0–6.0
Industry not reported (990)	10		
All other industries	81		
Total	169		
Occupation			
Farmers, except horticulture (473)	75	8.1	6.4–10.2
Occupation not reported (999)	9		
All other occupations	85		
Total	169		

Includes data from 26 states: Alaska (1987–1988); Colorado, Georgia, Kansas, Kentucky, Nevada, Rhode Island, South Carolina, Utah, and Wisconsin (1985–1999); Hawaii (1993–1994, 1996, 1998–1999); Idaho (1988–1999); Indiana (1986–1993, 1995, 1998–1999); Maine (1985–1996, 1998); Missouri (1985–1986); Nebraska (1985, 1999); New Hampshire (1985–1996, 1998–1999); New Jersey (1988–1999); New Mexico (1986–1999); North Carolina (1987–1999); Ohio (1985–1993, 1995–1998); Oklahoma (1985–1993); Tennessee (1985–1988); Vermont (1986–1999); Washington (1989–1992); West Virginia (1988–1999) (12).

smokers'' compared to no cases among ''current smokers,'' suggesting a possible protective effect of cigarette smoking against farmers' lung disease [Gruchow et al., 1981]. The mechanisms of this phenomenon are not well understood, but could include smoking-induced alterations of lung-defense mechanisms or immunologic reactivity with depression of immune responses to antigens delivered to the lung, which are well documented to occur in smokers [Finklea et al., 1971; Selman, 2003]. A recent study reported an inhibitory (and possibly protective) effect of nicotine in cigarette smoke on HP [Blanchet et al., 2004]. We were unable to evaluate decedents' smoking patterns over time, since smoking status is not available on death certificates. The effects of smoking on HP mortality are probably complex and controversial. For example, smoking may have an adverse effect on the clinical course of HP. A study on the clinical prognosis of farmer's lung disease reported that the 10-year survival rates were 70.7% in smokers, versus 91.5% in nonsmokers ($P<0.05$) [Ohtsuka et al., 1995]. However, it seems unlikely that reduced smoking prevalence of the magnitude that occurred in U.S. adults could account by itself for the observed increases in HP mortality, even if it did contribute.

In this study, 37.3% (n = 304) of HP deaths were coded as farmer's lung and 55.5% (n = 452) were coded as HP due to unspecified organic dust. Geographically, the HP age-adjusted death rates were higher in counties with extensive and/or concentrated agricultural activities (Fig. 2). Wisconsin had nearly 12% (n = 94) of the total HP deaths, the highest death rate (1.04 per million), and approximately 25% (n = 77) of all deaths with farmer's lung. Of these 77 farmer's lung deaths, the usual occupation in 21 cases was *farmers, except horticulture*, the same of 11 of 12 decedents in the highest mortality counties of Dane, Jefferson, and Vernon. This region has a relatively high proportion of dairy production and farms, where exposure to a broad spectrum of antigens is likely to occur. In this setting, exposure to *Saccharopolyspora rectivirgula* is especially important [Schuyler et al., 1997]. In 2002, there were about 4,330 farm workers in Wisconsin [U.S. Department of Labor, 2002] and a survey of 1,045 dairy farmers in the central part of the state reported a farmer's lung disease prevalence of 8.5% [Marx et al., 1978]. Farmer's lung cases associated with mortality probably represent only a fraction of the total burden of disease. In Finland, Kokkarinen et al. [1994] reported 13 fatal cases of farmer's lung between 1980 and 1990, representing a mortality rate of approximately 1%. Three long-term follow-up studies described farmer's lung-associated mortality ranging from 9 to 17% [Emanuel et al., 1964; Barbee et al., 1968, 1979].

Industries and occupations with elevated PMR in this study included agricultural production and farmers, respectively. Our findings are consistent with other studies involving farmers [Campbell, 1932; Dickie and Rankin, 1958], sugar cane workers [Buechner et al., 1958], and mushroom handlers [Cox et al., 1988; Moore et al., 2005]. Agricultural workers are at risk for HP because they are potentially exposed to various organic dusts, animal proteins, avian proteins, insect products, and vegetable derivatives [Christiani, 2005]. However, there is a broad range of other agents and industries associated with the development of HP. One such industry is chemical manufacturing and processing, especially when isocyanates and anhydrides are used for paint spraying and epoxy manufacture [Fink and Schlueter, 1978]. HP due to low-molecular weight agents such as toluene diisocyanate and trimellitic anhydride is well recognized mainly in Japan [Yoshizawa et al., 1999; Selman, 2003; Christiani, 2005]. Under ICD-9, HP due to low-molecular weight agents could have been coded as ''Unspecified allergic alveolitis and pneumonitis (495.9)'' [U.S. Department of Health and Human Services, 1988]. However, under ICD-10, HP code J67 specifically excludes ''pneumonitis due to inhalation of chemicals, gases, fumes or vapours'' and instructs that such cases be coded in J68 (''Respiratory conditions due to inhalation of chemicals, gases, fumes and vapours'') [World Health Organization, 1992]. Unfortunately, code J68 [World Health Organization, 1992] also does not include a separate sub-classification for HP. Thus, it is likely that HP due to low-molecular weight agents will be under-represented under the current ICD-10 coding system.

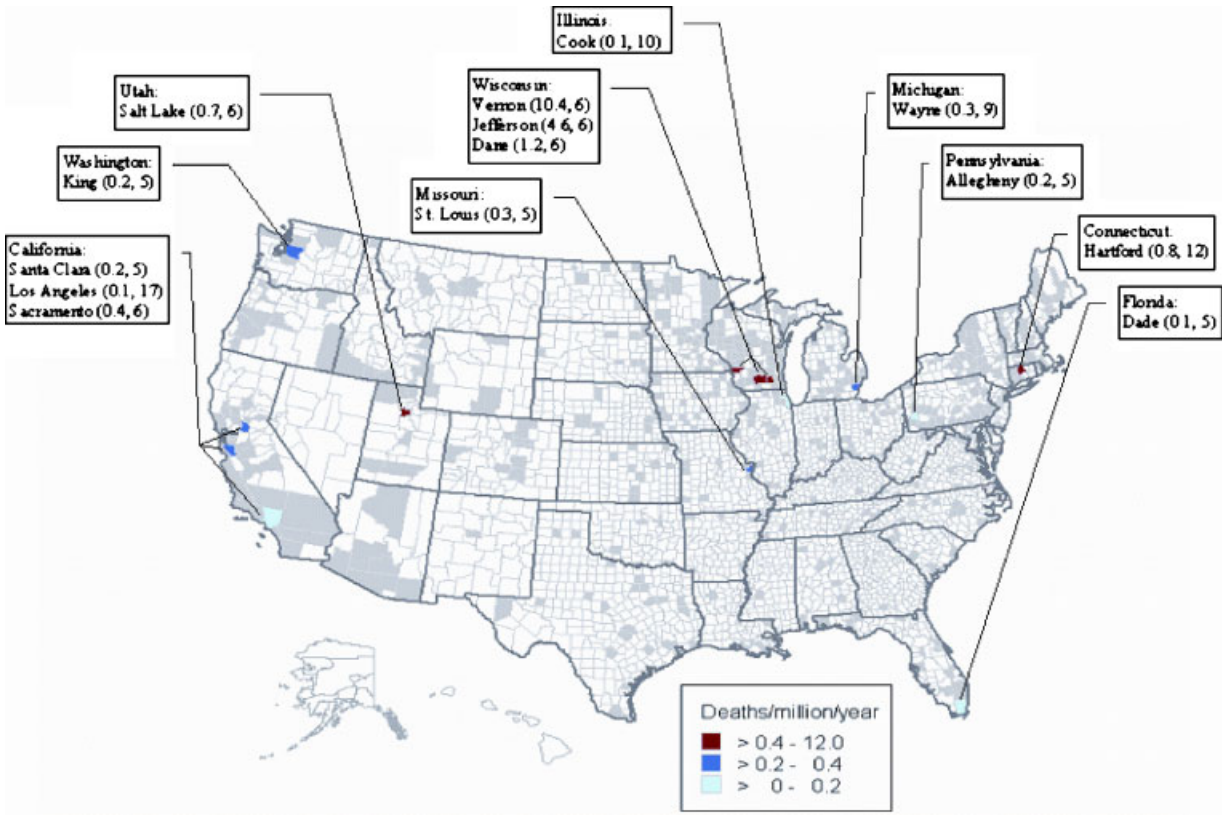

FIGURE 2. Age-adjusted HP death rate (per million per year) and number of deaths, by county, United States, U.S. residents aged ≥15 years, 1980–2002. Gray areas are counties with 1–4 deaths where age-adjusted rates were not calculated. White areas are those counties with no deaths.

Most individuals develop HP through exposure to agricultural or industrial environments [Fink, 1986; Mohr, 2004; Beckett et al., 2005]. In addition, HP can also occur in home and office occupants through forced-air heating, humidification, or air-conditioning systems [Banaszak et al., 1970; Kreiss and Hodgson, 1984; Fink, 1986]. For example, an evaluation of workers in one office environment served by a contaminated forced-air system revealed an HP rate of 15% [Banaszak et al., 1970].

Our analysis demonstrated that nearly 56% of HP deaths were due to unspecified organic dust, which may be suggestive of a high proportion of HP without sufficient information on exposures to etiological agents.

There are some limitations to this study. First, we were not able to evaluate specific information on exposure to potentially causative agents because these data are not recorded on the death certificates. Second, information on occupations and industries from death certificates was available only for certain years and certain states. Thus, the PMRs only reflect the industrial and occupational profiles of those states in those years. In addition, the usual industry and occupation recorded on each death certificate may not have been the industry and occupation in which the decedent's causative exposure occurred. Third, because of potential migration factors, the state of residence at death does not always match the state in which the decedents' causative exposure occurred. Fourth, states with better surveillance programs may impact more identifications of HP in terms of specific occupations and exposures. For example, the reason why Wisconsin has the highest overall mortality rate might be related with continuous studies on Farmer's lung by the Marshfield Clinic in this state for over 20 years. Fifth, reliability of the death certificate diagnosis is unknown and inaccuracies of death certificate diagnoses might not be equally inaccurate over different geographic areas. This is particularly true given the difficulty in making the diagnosis of HP and its relative rarity as compared to a disease like asthma. Sixth, the low fatality rate for HP mortality may not be a good index of overall incidence. Also, as noted previously, smoking information on each death certificate was unavailable, precluding any examination of the association between smoking and HP; there could be potential misclassification of HP; and the way that ICD-10 codes are defined prevent capture of HP cases due to low-molecular weight agents in death certificate data coded under ICD-10.

Despite these limitations, the national mortality data offer substantial benefits: they are national in scope, well-documented, and readily available. They are used to provide historical perspective on HP mortality and can provide useful information on HP by location, industry, and occupation, suggesting ways in which to target preventive intervention and disease-management resources.

It is currently unclear what factors account for the increasing death rate over the period 1980–2002. Additional epidemiological and surveillance research would be needed to identify the factors that contributed to HP mortality and morbidity. In 2004, the National Heart, Lung, and Blood Institute Workshop Committee on HP recommended that better documentation of the prevalence of HP in the population and improved criteria for diagnosis are needed to provide additional insights into environmental, occupational, and clinical characterization of HP cases [Fink et al., 2005]. The death rate was greater in farming states, where farmer's lung accounted for nearly 40% of all HP deaths. Regional prevention and control strategies in high-risk industries (e.g., agricultural production) and occupations (e.g., farmers) are needed. Primary prevention strategies (for reduction of exposures to causative agents), and secondary prevention strategies (for early recognition of HP in workers exposed to antigens) are needed. Effective primary prevention strategies include reducing exposure through changes in work practices, such as substituting methods of storing forage that do not cause mold formation [Kryda and Emanuel, 1986], or minimizing exposures with engineering controls [Christiani, 2005].

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