Environmental Research Section A **83,** 67–71 (2000)
doi:10.1006/enrs.1999.4032, available online at http://www/idealibrary.com on IDEAL®

A Model for Predicting the Frequency of High Pesticide Exposure Events in the Agricultural Health Study

David T. Mage,*[,1] Michael C. R. Alavanja,† Dale P. Sandler,‡ Cheryl J. McDonnell,§ Burt Kross,¶ Andrew Rowland,‡ and Aaron Blair†

**U.S. Environmental Protection Agency, National Center for Environmental Assessment, MD-52, Research Triangle Park, North Carolina 27711; †Epidemiology and Statistics Program, National Cancer Institute, Bethesda, Maryland; ‡National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina; §SRA Technologies, Inc., Falls Church, Vrginia; and ¶University of Iowa, Iowa City, Iowa*

Received April 22, 1999

The frequency of self-reported high pesticide exposure events (HPEE) has been recorded in the NCI/EPA/NIEHS Agricultural Health Study (AHS). Fourteen percent (14%) of the enrolled applicators responding reported "an incident or experience while using *any* pesticide which caused an unusually high exposure." These data show, as expected, that the probability of a report of an HPEE increases with the cumulative number of days of pesticide application reported by the applicator. We have developed a three-parameter model that predicts the risk odds ratio (OR) of an HPEE as a function of the number of days that pesticides are applied. These events are costly in terms of resulting health-care visits, lost time from work, and potential risk for cancer and other chronic diseases. We propose that failure to carefully follow all the pesticide manufacturer's label requirements, inexperience, and random events (i.e., breaking hose) are the three factors responsible for the events observed. Special precautions for new or infrequent users of pesticides are indicated.

Key Words: **pesticides; pesticide poisoning; accidental exposures; farmers; exposure assessment.**

INTRODUCTION

Agricultural activity, involving machinery operation (threshing, harvesting, . . .) and chemical applications (pesticides, fungicides, . . .), is recognized as one of the most dangerous classes of occupations in the United States (National Institute of Occupational Safety and Health, 1998). Although some studies have examined qualitatively the factors leading to trauma-type injury in terms of risk factors and odds ratios (e.g., National Committee for Injury Prevention and Control, 1989; Pratt *et al.*, 1992), Lyman *et al.* (1999) found that "there have been no reports of the lifetime prevalence of prior agricultural injury among active farmers." The prospective Agricultural Health Study (AHS), conducted by NCI, EPA, and NIEHS, is a comprehensive study that is relating qualitative and categorical responses to questionnaires, about agricultural practices involving pesticide handling, to lifetime exposures to pesticides and subsequent health outcomes (Alavanja *et al.*, 1996, 1999a). This paper examines one of those outcomes, the lifetime prevalence of high pesticide exposure events (HPEE) reported by the AHS cohort, and it develops a quantitative model to explain the data set that we have reported in a companion paper (Alavanja *et al.*, 1999b).

METHODS

The AHS cohort includes 60,000 licensed pesticide applicators in the states of Iowa and North Carolina who have completed a general enrollment questionnaire (Alavanja *et al.*, 1996, 1998). Thirty-eight percent (38%) of the AHS members completed a supplementary questionnaire that provides a more detailed application-history data set (Tarone *et al.*, 1997). A

This paper has been reviewed for technical accuracy by the U.S. Environmental Protection Agency. It does not necessarily represent Agency policy.

Human Subject Clearance: The Agricultural Health Study is being conducted in accordance with NIH and EPA institutional guidelines for the protection of human subjects. All information presented has been collected with survey instruments approved by the U.S. Office of Management and Budget under the terms of the Paperwork Reduction Act.

[1]To whom correspondence should be addressed. Fax: (215) 204-7486. E-mail: davidm@temss2.isr.temple.edu.

0013-9351/00 $35.00

companion paper analyzed the characteristics of these 22,884 members, including those 3231 self-reporting at least one HPEE (Alavanja *et al.*, 1999b). This paper extends that work by modeling the increase in risk of having at least one HPEE with increasing pesticide application activity (which can include handling, mixing, loading, clean up, and waste disposal on the day of application).

It is a truism that the risk of having at least one HPEE must increase with the number of applications of pesticides that the farmer may make in a lifetime career, which we model in this paper. In theory, the applicator of a registered pesticide who carefully follows all the manufacturer's label requirements (MLRs) and properly uses all MLR personal protective equipment (PPE), such as the specified type of glove, may have minor contact with a pesticide, but will not have an HPEE. Accidental potentially high exposure situations during application (e.g., spray from broken hose, PPE torn on a sharp object) can occur on any given day. However, with the proper PPE in careful use, the major pesticide contact should be with the intact outer covering of the PPE, not with the applicator's skin. Consequently, we assume that no HPEE occurs either if all the MLRs are carefully followed *or* if no accident occurs even if the MLRs are not followed. This is the basis for our probability model.

The method we chose is to model the AHS cohort as dichotomous: Let some applicators always carefully follow the MLRs while others do not always follow them. We assume that only those applicators who do not carefully follow the MLRs are at risk of an HPEE. Therefore, the probability of having at least one HPEE must increase with the number of days of pesticide application, only among those who are at risk (i.e., not carefully following the MLRs). We let $p(n)$ represent the probability of an HPEE on an at-risk applicator's nth application day, and $1 - p(n)$ represent the probability that there is no HPEE on that nth day. Pesticide handling and application are complicated procedures, requiring both strength and skill, and there is a learning period in which experience is gained on how to operate the equipment properly and apply the pesticides safely. That experience should result in less risk of an HPEE in subsequent applications. We therefore model the probability of an occupational HPEE as $p(n) = a + b/n$, where n is the ordinal day of lifetime pesticide application and a and b are parameters evaluated by a least-squares fit to the AHS data we reported previously (Alavanja *et al.*, 1999b).

Parameter a represents the constant risk of a potential HPEE unavoidable accident from random causes and circumstances beyond the control and skill of the applicator (e.g., spray from a broken hose, gust of wind). The term b/n represents an additional risk of a preventable HPEE that decreases as the applicator gains experience and becomes more adept at handling pesticides (e.g., by pouring without splashing). This type of learning process, with a decrease in avoidable accident rate with experience, also occurs in other licensed fields, such as piloting aircraft and driving motor vehicles (Williams, 1996).

RESULTS

Table 1, column 2, shows the percentage of the AHS cohort who reported applying pesticides for the number of days shown in column 1. Of the total respon-

TABLE 1
Comparison of Predicted Odds Ratio for at Least One HPEE by a Model of the AHS Data

Total number of days pesticides applied by AHS farmers (n)	Percentage (**P**) of applicators in this range of days	Odds ratio (95% CI) of at least one HPEE referenced to the 25- to 55-day cohort	Odds ratio predicted by our three-parameter model	Average of $(1-P)$ the probability of an at-risk applicator to have ≥ 1 HPEE
1 to 24	21.9	1.06[a] (0.76–1.14)	0.632	0.146
25 to 55	8.4	1.00 (reference)	1.00	0.230
56 to 107	8.1	1.34 (1.10–1.61)	1.31	0.310
108 to 149	10.3	1.62 (1.37–1.91)	1.58	0.364
150 to 209	5.3	1.86 (1.52–2.27)	1.83	0.421
210 to 366	14.0	2.20 (1.89–2.54)	2.25	0.519
367 to 449	7.7	2.53 (2.13–2.98)	2.63	0.607
450 to 524	9.7	3.06 (2.62–3.56)	2.84	0.655
525 to 1499	10.9	3.48 (2.99–4.01)	3.62	0.835
1500 to 4500	3.7	4.32 (3.54–5.23)	4.27	0.985

Note. Source of data: Alavanja *et al.* (1999b).
[a]Not used in the model-fitting procedure. See discussion in text.

dents, one-seventh (14%) of the cohort reported having at least one HPEE during their farming career. Because it was considered unreasonable to ask the applicators to recall the exact number of days and years they applied pesticides in their careers, and because of coding limitations, each applicator was asked to choose which of several grouped categories best described their application history.

Responses to years of application and days per year were used to assign applicators to categories of the combined variables, application days. For example, the applicators who responded that they applied pesticides between 2 and 4 days per year, and had been farming between 2 and 5 years, could have had between 4 and 20 career applications. The entire data set was analyzed and such responses were assigned to different ranges of lifetime days of application, as reported in Alavanja *et al.* (1999b).

Table 1, column 3, gives the observed relative risk odds ratio (OR) and confidence interval for each grouping of numbers of days of applications in Table 2 of Alavanja *et al.* (1999b). The probability of at least one HPEE, for an applicator not carefully using all the required PPE, is expected to increase with the number of days of application, in a similar way as the probability of winning at least once when playing roulette increases with the numbers of spins of the wheel. However, we observed an anomalous decrease in OR for the second-row cohort applying pesticides 25–55 days, which is discussed later in this paper. Therefore, the rate of HPEE in the second-row cohort is used as reference (OR = 1) for comparing the total percentages of those applicators having at least one high pesticide exposure incident, as shown in column 3 of Table 1.

To model the risk of an HPEE we computed the probability of having at least one accident after n days of application. Because the probability of avoiding an HPEE on day n is $[1 - (a + b/n)]$, the probability of never having an HPEE through the completion of the application on day n is $P(n) = [1 - (a + b/1)]\,[1 - (a + b/2)]\,[1 - (a + b/3)] \ldots [1 - (a + b/n)]$. Therefore, the probability of having at least one HPEE at the end of day n is equal to $1 - P(n)$. To compute the average probability for the cohort of those reporting an HPEE, with the number of days of application shown in Table 1, the probabilities were integrated over the range to compute the average probability of an HPEE for all the days in the range interval. This is equivalent to assuming that all the applicators falling into a range were uniformly distributed across the days in that range. A least-squares optimization was performed to give the values of $a = 0.01528$ and $b = 0.0468$ day that minimized the sum of the squares between the OR predicted and the OR observed (sum = 0.0879) for $56 < n < 4500$ days, referenced to an OR = 1 between 25 and 55 days. The predicted OR values in column 4 of Table 1 are all very close to the observed OR values, and the deviations between these values have no consistent pattern. The sum of $a + b = 0.0622$ represents the probability of an at-risk applicator having an HPEE on the very first day of application of a registered pesticide.

The AHS cohort of 22,864 applicators was then evaluated as having a fraction of x at-risk applicators whose risk of an HPEE on day n is described by our model as $a + b/n$ and a complementary fraction of applicators $(1 - x)$ who have zero risk because they exercise due care and conform to all MLRs. We estimated the number of at-risk applicators (6911) by solving for the value of x using the values in Table 1, columns 2 and 5, as follows:

1. The number of at-risk applicators is $22{,}864x$.
2. The number of HPEEs for those applying from 1 to 24 days is $(22{,}864x)$ (0.219) (0.146) (1.06*/0.632), where 1.06*/0.632 adjusts for the singular discrepancy between the actual and predicted odds ratio.
3. The predicted number of HPEEs for those applying from 25 to 55 days is $(22{,}864x)$ (0.084) (0.230), and this computation is continued for all groupings.
4. Solve for $3231/[22{,}864 \sum \mathbf{P}\,(1 - P)]$, where $\sum \mathbf{P}(1 - P)$ is the sum of all products of percentage terms ($\mathbf{P}$) in column 2 and average probability terms $(1 - P)$ in column 5 of Table 1, with the corrections noted in step 2 above.

Using this procedure, given 3231 reports of at least one HPEE, we predict this number for a value of $x = 0.3023$, implying that approximately 70% of the AHS cohort follow all the MLRs and use all PPEs correctly and that 30% of the cohort do not do so.

DISCUSSION

We noted in Table 1 (see footnote [a]) the anomalous decrease in OR when going from 1 to 24 days of appli-

TABLE 2

Modeled Decrease of Risk of an HPEE with Increasing Experience (n), Relative to a Risk of 1 on the First Day of Application ($n = 1$), for at-Risk Applicators

Relative risk	1	0.627	0.497	0.434	0.396	0.321	0.261	0.253	0.247	0.246
Day n	1	2	3	4	5	10	50	100	1000	∞

cation to 25 to 55 days of application. Such a decrease in risk with increasing applications could occur from (1) some novice applicators deciding to follow carefully all the MLRs, perhaps induced by a near-HPEE incident; (2) licensed applicators who only apply pesticides infrequently, without the learning benefit of more frequent application [e.g., once per year nonfarm application of a registered pesticide (license required) by an orchid grower], and (3) classical sampling error.

Table 2 shows the predicted decreasing probability of an HPEE with increasing experience, for an at-risk applicator with a continuous learning curve, with a relative risk set at one on day $n = 1$. The model predicts that, with experience, an at-risk applicator will have about half the risk of an HPEE on the third day compared to that on the first application day and one-third of the first-day risk on the 10th day, and by the 100th day, the risk will have fallen toward the asymptote of one-fourth of the first-day risk.

We recognize that several possible host factors may be involved as HPEE risk factors. For example, lower economic status (use of older equipment requiring more repair) and any mental or physical disabilities (e.g., depression or loss of balance) may increase the applicator's risk of an HPEE. We previously identified work practices more common among the AHS cohort who reported at least one HPEE than for those who did not report any HPEE as delay in changing clothing or washing after pesticide application; mixing clothing worn during pesticide application with the family wash; washing up inside the home after application; applying pesticides within 50 yards of their well; and storing pesticides in the home (Alavanja *et al.*, 1999b). Some of these poor personal hygiene practices may not directly cause an HPEE during application, but they may be indicative of an applicator's attitude of following the MLRs and what is considered an acceptable risk. Lyman *et al.* (1999) identified alcohol consumption, fatigue, and hurry-when-farming as significant predictors of prior mechanical injury. These three factors also may lead to inattention during an application resulting in an HPEE. Nonhost factors such as a break in a hose line causing an accidental spray of pesticide on the applicator or a sudden gust of wind causing the applicator to become caught in the application spray are those risk factors that remain approximately constant with time while the applicator is gaining experience in following the MLRs. We are currently investigating the recorded set of host factors involving applications for those that may be different between the 14% of our cohort who experienced HPEEs and those who did not.

Our model of the AHS cohort implies that for every 1000 applicators making their very first application, 698 will be following all the MLRs carefully and 302 will be at risk of an HPEE from not following all the MLRs with care. The model predicts that more than 18 HPEEs would occur on the very first day in the group of 302 at-risk applicators [$18 < 302\ (a + b/1) = 302\ (0.0622)$], and, with practice, this rate will approach an asymptote of 4.5 HPEEs per 1000 applications by a fully experienced cohort. If our model is correct, the occurrence of all these HPEEs may be preventable if all the MLRs are followed carefully and the specified PPE is in good condition and used properly. This model points out the need for more rigorous training of pesticide applicators to follow the MLRs and a need to warn the beginners and infrequent users to be especially alert during applications because of their inexperience with practical field conditions.

This model also has important implications for exposure assessments in agricultural epidemiology. The applicators would appear to have the highest annual exposures to pesticides during their earliest years of farming while still learning and perfecting the skills involved in pesticide application. We have shown (Alavanja *et al.*, 1998) that HPEEs may lead to increases in reports of acute symptoms and health-care visits. In addition, because many cancers have a decades-long latency period before discovery, current pesticide exposure measurements may seriously underpredict the exposures that may have occurred earlier in the applicators' careers which could have initiated or promoted a recorded cancer. Consequently, when performing an exposure assessment of pesticide applicators, the number of years of active farming may be an important variable to consider in stratification of an exposure sample. This could ensure that novice applicators, who may be most at risk of high exposures, are also included in the sample.

ACKNOWLEDGMENTS

This work was supported by NIH Contracts N01-CP-33047, N01-CP-33048, and N01-CP-21905.

REFERENCES

Alavanja, M. C. R., Sandler, D. P., McMaster, S. B., McDonnell, C. J., Lynch, C. F., Pennybacker, M. R., Zahm, S. H., Rothman, N., Dosemeci, M., Bond, A., and Blair, A. (1996). The Agricultural Health Study. *Environ. Health Perspect.* **104,** 362–369.

Alavanja, M. C. R., Sandler, D. P., McDonnell, C. J., Lynch, C. F., Pennybacker, M. R., Zahm, S. H., Mage, D. T., Steen, W. C., and Blair, A. (1998). Factors associated with pesticide-induced visits to health care facilities in the Agricultural Health Study. *Environ. Health Perspect.* **106,** 415–420.

Alavanja, M. C. R., Sandler, D. P., McDonnell, C. J., Lynch, C. F., Pennybacker, M. R., Zahm, S. H., Mage, D. T., Steen, W. C., Wintersteen, W., and Blair, A. (1999a). Characteristics of pesticide use in a pesticide applicator cohort: The Agricultural Health Study. *Environ. Res.* **80**(Section A), 172–179.

Alavanja, M. C. R., Sandler, D. P., McDonnell, C. J., Mage, D. T., Kross, B. C., Rowland, A. S., and Blair, A. (1999b). Characteristics of persons who self-reported a high pesticide exposure event in the Agricultural Health Study. *Environ. Res.* **80**(Section A), 415–420.

Lyman, S., McGwin, G., Jr., Enochs, R., and Roseman, J. M. (1999). History of agricultural injury among farmers in Alabama and Mississippi: Prevalence, characteristics, and associated factors. *Am. J. Ind. Med.* **35,** 499–510.

National Committee for Injury Prevention and Control (1989). "Injury Prevention: Meeting the Challenge." Oxford Univ. Press, New York.

National Institute for Occupational Safety and Health (1998). NIOSH facts. Agricultural Safety and Health. http://www.cdc.gov/niosh/agfc.html.

Pratt, D. S., Marvel, L. H., Darrow, D., Stallones, L., May, J. J., and Jenkins, P. (1992). The dangers of dairy farming: The injury experience of 600 workers followed for two years. *Am. J. Ind. Med.* **21,** 637–650.

Tarone, R., Alavanja, M. C. R., Zahm, S. H., Lubin, J. H., Sandler, D. P., McMaster, S. B., Rothman, N., and Blair, A. (1997). The Agricultural Health Study: Factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am. J. Ind. Med.* **31,** 233–242.

Williams, A. F. (1996). Magnitude and characteristics of the young driver crash problem in the United States. *In* "New to the Road: Reducing the Risks for Young Motorists" (H. Simpson, Ed.), pp. 79–96. Univ. California Press, Los Angeles.