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Charles Breckenridge, Ph.D.
Sci. and Tech. Sr. Res. Fellow
P.O. Box 18300
Greensboro NC 27419-8300

Telephone: (336) 632-7082
Email: charles.breckenridge@syngenta.com

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November 23, 2004

Dr. C. W. Jameson
National Toxicology Program Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
PO Box 12233
Research Triangle Park, NC 27709
jameson@niehs.nih.gov

Subject: Department of Health and Human Services. Public Health Service. National Toxicology Program; Call for Additional Public Comments on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition. Federal Register Notice Vol. 69, No.205/Monday October 25, 2004; 62276-62279.

Dear Dr. Jameson:

On July 19, 2004, Syngenta submitted a letter plus nine attachments in response Federal Register Notice call for public comment by the Department of Health and Human Services, Public Health Service, National Toxicology Program on 21 Substances, Mixtures and Exposure Circumstances Proposed for Listing in the Report on Carcinogens, Twelfth Edition (Federal Register Notice Vol. 69, No. 97/Wednesday, May 19, 2004; 28940-28944). On October 25, 2004 the public comment period on this proposal was reopened (see subject Federal Register Notice)

In response to this second notice, Syngenta wishes to request that the comments provided in our July 19th letter be considered. In addition, since July, the following three documents have been completed and are included as Attachments (1-3) with this letter.

1. NCI publication (Rusiecki et al., 2004) on the cancer incidence of pesticide applicators exposed to atrazine.
2. A critical review of the Rusiecki et al, 2004 study by Dr. Jack Mandel.
3. A review by EPA (Dr. Jerry Blondell) of Syngenta's nested case-control study on atrazine.

A summary of our previously stated position incorporating the new information follows:

Atrazine does not meet the NTP criteria as an agent that is either "known to be human a carcinogen" or as an agent that "may be reasonably anticipated to be a human carcinogen.

Epidemiology Evidence

- The epidemiological evidence reviewed by EPA, IARC and independent experts (Delzell et al., 2004) have not found any credible evidence of a causal association between atrazine exposure and human cancer.
- This conclusion is reinforced by the 2004 publication on cancer incidence data for atrazine applicators in the Agricultural Health Study (Rusiecki, et al., 2004; Attachment 1) The Agricultural Health Study is a government sponsored study being conducted by the National Institute of Health, the National Cancer Institute, the National Institute of Environmental Health Science and the Environmental Protection Agency. The authors of this most recent study state that “We found no association between cancer incidence and atrazine exposure, whether atrazine was analyzed as a cumulative measure (lifetime days of exposure) or as an intensity-weighted cumulative measure (intensity-weighted lifetime days of exposure).” See Mandel, 2004 (Attachment 2) for a critical review of this study.
- Rusiecki et al., (2004) also reported that relative risk ratios for prostate cancer ranged from 0.75 to 0.88 and 0.86 to 1.03, respectively, for lifetime days of atrazine exposure or intensity-weighted days atrazine exposure. These new data confirm the previous publication (Alavanja et al, 2003) that found no association between prostate cancer incidence and atrazine exposure.
- EPA (Dr. Blondell, October 21, 2004 – Attachment 3) recently reviewed the nested case-control study (published by Hessel et al., 2004), of prostate cancer in the Syngenta atrazine production facility located in St. Gabriel, LA. He concluded that the results “did not support a finding of association between prostate cancer and atrazine exposure” ... nor was atrazine “ a likely cause of prostate cancer”.

Alavanja et al., 2003 and Hessel et al., 2004 were referenced in our earlier submission but are also included as Attachments 4 and 5 for reference.

Animal Evidence: Mode of Action

- Neither atrazine nor its chlorotriazine metabolites are structurally related to any agent known to be a human carcinogen or reasonably anticipated to be a human carcinogen.
- Atrazine is not genotoxic, directly estrogenic or androgenic
- Atrazine does not induce aromatase in the intact animal.
- Key events underlying the occurrence of mammary tumors in the female Sprague-Dawley rat are well defined.
- The sequence of events leading to mammary tumor development in female SD rats is temporally coherent.
- The mode of action is biologically plausible for the rat but not relevant to humans
- A dose-response assessment has been conducted for each key event in the female SD rat;
- The biological basis for the existence of a threshold for the critical key event (estrus cycle disruption) observed in the SD rat has been defined.

- The mode of action underlying the carcinogenic response, observed only at high doses in a highly susceptible strain of rat, in one sex and one organ, is well understood with respect key events, dose response, and temporal consistency.

Relevance of the Mode of Action to Man

- The mode of action underlying the carcinogenic response observed in the female Sprague-Dawley rat was concluded by EPA (2000, 2003), IARC (1999) and Australia (1997) to be not relevant to humans.

Atrazine Cancer Classification: EU, Australia, IARC, EPA

Various authoritative bodies around the world have ruled as recently as 2003 that atrazine is not likely to be carcinogenic to humans (See table below). In the absence of substantive new data, as discussed previously, the National Toxicology Program is not justified for nominating atrazine for consideration for listing as a carcinogen.

As a note, contrary to incorrect information often cited regarding European bans of atrazine, the decision not to include atrazine in the European Union Annex I listing was due to a non-health based water standard which had been exceeded in the past mainly due to use patterns and higher rates no longer used. In fact, the science review conducted for the European Union by regulatory officials in the United Kingdom concluded that, "It is expected that the use of atrazine, consistent with good plant protection practice, will not have any harmful effects on human or animal health or any unacceptable effect on the environment." In Europe, a closely related triazine, is widely used for weed control in corn.

Table 1: Summary of Atrazine Risk Assessment Profile

	EU-UK (1996)	Australia (1997)	IARC (1999)	EPA (2000/03)
Genotoxicity	Not Mutagenic in Standard Studies	Not Genotoxic	Not Genotoxic	Not Genotoxic
Animal Evidence	Mammary - Female SD Rat	Mammary - Female SD Rat	Mammary - Female SD Rat	Mammary - Female SD Rat
Mode of Action (MOA)	Endocrine MOA	MOA Unique to Female SD Rat	MOA Unique to Female SD Rat	MOA Unique to Female SD Rat
Relevance	Not relevant to Humans	Not relevant to Humans	Not relevant to Humans	Not relevant to Humans
Epidemiology	Not Evaluated	Inconclusive	Inadequate Evidence	Human Cancer Risk Not Likely
Classification	Case for Non-Classification	None	Not Classifiable Group 3	Not Likely to be Carcinogenic in Humans

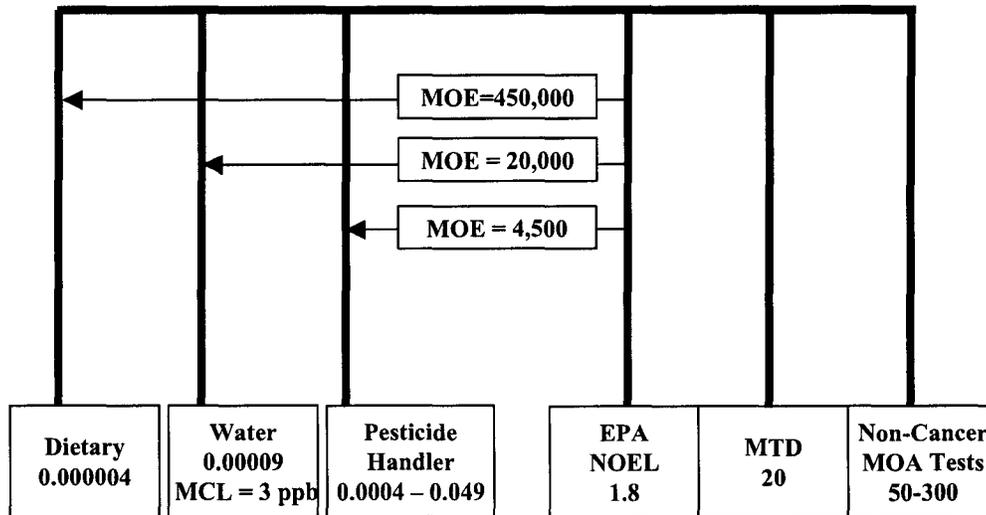
Potential for Human Exposure via Water

In recent years, out of the 54,000 community water systems on ground or surface water in the US, there have been 0 to 5 community water systems receiving notices of violation annually for the atrazine MCL of 3 ppb. This low number of exceedances is attributed to atrazine watershed and label mitigation measures that were put in place in the early 1990s and were more fully adopted by growers after 1995 as well as changes in use patterns and stewardship practices. Atrazine levels in water are declining as documented by USGS and others. Currently there are no active community water systems with atrazine multi-year period averages greater than 3 ppb. In January, 2003, EPA established drinking water levels of concern for total chlorotriazine (parent plus chloro-metabolites) These DWLOCS ranged from 12.5 to 68 ppb (See Table 2).

Table 2: Summary of Lowest Drinking Water Levels of Comparison (DWLOC) for Atrazine and its Chlorinated Metabolites from EPA-OPP Interim Registration Eligibility Decision (IRED), January 31, 2003

Population Subgroup	Intermediate (Seasonal) Chronic (Annual) Exposure (ppb)	
	90-day	Annual
General Population	-	68
Infants <1 year old	12.5/37.5	12.5
Children 1 to 6	-	23
Children 7 to 12	-	53
Females 13 to 50	-	60
Males 13 to 19	-	68
Males 20 and over	-	68
Seniors	-	68

As part of the May, 2004 Memorandum of Agreement between EPA and all technical atrazine registrants, any community water system that receives a notice of violation for exceedance of the atrazine MCL or any community water system that exceeds a 90-day trigger for EPA's Drinking Water Levels of Concern (DWLOC) for atrazine and its metabolites will enter into site specific management plans to ensure that levels remain below standards.



Scale $\text{Log}_{(10)}$ (mg/kg/day)

NTP Process

The process document for the 12th RoC indicates that: "Nominations must contain a rationale for the review and, when possible, the appropriate background information and relevant data (e.g., journal articles, NTP Technical Reports, International Agency for Research on Cancer listings, exposure surveys, release inventories, etc.) that support the rationale."

The basis for the nomination of atrazine listed in the Federal Register does not follow the requirements for the nomination rationale. Rather the nomination cites as its basis an incomplete IARC finding of sufficient evidence of carcinogenicity in animals. The IARC finding actually states: "while there was sufficient evidence for carcinogenicity in the SD rat, after considering the atrazine mode of action research, the IARC concluded that there was strong evidence that the mechanism responsible for mammary tumor formation in the Sprague-Dawley rat is not relevant to humans."

It is Syngenta's understanding that the RoC Nomination Review Committee will meet only after the close of this comment period to determine whether the nomination goes forward. Therefore the evaluation by the NIEHS/NTP RoC Nomination Review Committee must be based on complete information, above and beyond the initial rationale, including the public comments to accurately assess "whether the information available for the nomination indicates a scientific justification for a review and warrants formal consideration by the NTP."

Other process considerations include the fact that EPA in 2003 completed a 9 year review and released in an Interim Reregistration Eligibility Document which concluded that atrazine in "not likely to cause cancer in humans." It is costly and duplicative to re-review the carcinogenicity potential of atrazine in light of this very recent and thorough review. NTP should remove atrazine from the nomination review in light of these recently completed comprehensive scientific evaluations and decisions.

Conclusions

Based upon this assessment, Syngenta concludes that NTP is not justified in proposing that atrazine be considered for listing in the 12th Report on Carcinogens. Syngenta requests that atrazine be removed from further consideration.

Sincerely,

[Redacted]



Charles Breckenridge, Ph.D.
Sci. and Tech. Senior Research Fellow
Syngenta Crop Protection, Inc.

Attachments

References/Attachments

1. Rusiecki, J.A., De Roos, A., Lee, W.J., Dosemeci, M., Lubin, H., Hoppin, J.A., Blair, A., & Alavanja, M.C.R. 2004, Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. *Journal of the National Cancer Institute* 96, 18, 1375-1382.
2. Mandel, J. Review of "Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. November 20, 2004.
3. Blondell, J. Review of a nested case-control study of prostate cancer and atrazine exposure. USEPA, Health Effects Division, October 21, 2004.
4. Alavanja, M.C.R., Samanic, C., Dosemeci, M., Lubin, J., Tarone, R., Lynch, C.F., Knott, C, Thomas, K., Hoppin, J.A., Barker, J., Coble, J., Sandler, D.P., & Blair, A., 2003. Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort. *American Journal of Epidemiology*, 157 (9), 800-814.
5. Hessel, P.A., Kalmes, R., Smith, T.J., Lau, E., Mink, P.J., & Mandel, J., A nested case-control study of prostate cancer and atrazine exposure. 2004. *Journal of Occupational and Environmental Medicine*, 46(4), 379-385.

Cancer Incidence Among Pesticide Applicators Exposed to Atrazine in the Agricultural Health Study

Jennifer A. Rusiecki, Anneclaire De Roos, Won Jin Lee, Mustafa Dosemeci, Jay H. Lubin, Jane A. Hoppin, Aaron Blair, Michael C. R. Alavanja

Background: Atrazine is the most heavily applied agricultural pesticide for crop production in the United States. Both animal and human studies have suggested that atrazine is possibly carcinogenic, but results have been mixed. We evaluated cancer incidence in atrazine-exposed pesticide applicators among 53 943 participants in the Agricultural Health Study, a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina. **Methods:** We obtained detailed pesticide exposure information using a self-administered questionnaire completed at the time of enrollment (1993–1997). Cancer incidence was followed through December 31, 2001. We used adjusted Poisson regression to calculate rate ratios (RRs) and 95% confidence intervals (CIs) of multiple types of cancer among atrazine exposed applicators. P_{trend} values were calculated using atrazine exposure as a continuous variable, and all statistical tests were two-sided. Two exposure metrics were used: quartiles of lifetime days of exposure and quartiles of intensity-weighted lifetime days of exposure. **Results:** 36 513 (68%) applicators reported ever using atrazine; exposure was not associated with overall cancer incidence. Comparisons of cancer incidence in applicators with the highest atrazine exposure and those with the lowest exposure, assessed by lifetime days (RR_{LD}) and intensity-weighted lifetime days ($RR_{IWL D}$) of exposure yielded the following results: prostate cancer, $RR_{LD} = 0.88$, 95% CI = 0.63 to 1.23, $P_{\text{trend}} = .26$, and $RR_{IWL D} = 0.89$, 95% CI = 0.63 to 1.25, $P_{\text{trend}} = .35$; lung cancer, $RR_{LD} = 1.91$, 95% CI = 0.93 to 3.94, $P_{\text{trend}} = .08$, and $RR_{IWL D} = 1.37$, 95% CI = 0.65 to 2.86, $P_{\text{trend}} = .19$; bladder cancer, $RR_{LD} = 3.06$, 95% CI = 0.86 to 10.81, $P_{\text{trend}} = .18$, and $RR_{IWL D} = 0.85$, 95% CI = 0.24 to 2.94, $P_{\text{trend}} = .71$; non-Hodgkin lymphoma, $RR_{LD} = 1.61$, 95% CI = 0.62 to 4.16, $P_{\text{trend}} = .35$, and $RR_{IWL D} = 1.75$, 95% CI = 0.73 to 4.20, $P_{\text{trend}} = .14$; and multiple myeloma, $RR_{LD} = 1.60$, 95% CI = 0.37 to 7.01, $P_{\text{trend}} = .41$, and $RR_{IWL D} = 2.17$, 95% CI = 0.45 to 10.32, $P_{\text{trend}} = .21$. **Conclusions:** Our analyses did not find any clear associations between atrazine exposure and any cancer analyzed. However, further studies are warranted for tumor types in which there was a suggestion of trend (lung, bladder, non-Hodgkin lymphoma, and multiple myeloma). [J Natl Cancer Inst 2004;96:1375–82]

Atrazine (2-chloro-4-ethylamino-6-isopropylamino)-s-triazine is a triazine herbicide that is used primarily on corn and soybean crops to control growth of broadleaf and grassy weeds. It is the most heavily used agricultural pesticide in the United States, with an estimated 76.4 million pounds applied annually (1). Human exposure to atrazine occurs occupationally in farming and manufacturing and environmentally through contaminated drinking water or drift. Atrazine is the most commonly detected pesticide in surface water in surveys in the midwestern United

States and was the second most frequently detected pesticide in the U.S. Environmental Protection Agency (EPA) National Survey of Pesticides in Drinking Water Wells (2). Use of atrazine has been restricted since 1993, primarily to protect water supplies (2). Only licensed pesticide applicators may purchase atrazine.

Results from animal and human studies on the carcinogenic effects of exposure to atrazine have been mixed. Oral administration of atrazine was associated with increased incidence and earlier onset of mammary tumors in female Sprague–Dawley rats but not in other strains of rats or in other mammals (3,4). Atrazine exposure was also associated with lymphomas and testicular cancer in rats and mice in some studies (5–7). Several epidemiologic studies in humans have evaluated cancer risks associated with atrazine exposure (8–22). Slightly greater than expected numbers of bladder, oral cavity, and lymphohematopoietic cancers were observed in a cohort of triazine herbicide manufacturing workers; however, none of the increases were statistically significant, and the people in the study were exposed to carcinogens other than atrazine (8). This study also found statistically significantly elevated standardized incidence ratios (SIRs) for prostate cancer (SIR = 3.94, 95% confidence interval [CI] = 1.28 to 9.20); however, this increase may have been due to the intensive prostate-specific antigen (PSA) screening of the workers in this cohort (8). A mortality study based on the same population also found an increased standardized mortality ratio for non-Hodgkin lymphoma (standardized mortality ratio = 3.72, 95% CI = 1.01 to 9.52) (9). However, no association was found between atrazine exposure and prostate cancer in a study by Alavanja et al. (10) of the Agricultural Health Study cohort, a cohort of pesticide applicators from Iowa and North Carolina enrolled from January 1, 1993, through December 31, 1997.

In case–control studies conducted in the midwestern United States, atrazine or triazine use was not associated with Hodgkin disease (11), leukemia (12), multiple myeloma (13), soft tissue sarcoma (11), or colon cancer (14). Atrazine use was weakly or

Affiliations of authors: Occupational and Environmental Epidemiology Branch (JAR, WJL, MD, AB, MCRA) and Biostatistics Branch (JHL), Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Rockville, MD; Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, and Department of Epidemiology, University of Washington, Seattle (ADR); Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, NC (JAH).

Correspondence to: Michael C. R. Alavanja, DrPH, Occupational and Environmental Epidemiology Branch, National Cancer Institute, 6120 Executive Blvd., EPS 8000, Bethesda, MD 20892-7240 (e-mail: alavanjm@mail.nih.gov).

See “Note” following “References.”

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moderately associated with non-Hodgkin lymphoma (NHL) in case-control studies conducted in Iowa and Minnesota (15), Kansas (11), and Nebraska (16,17), although the association in the Nebraska study was diminished after adjustment for exposure to 2,4-dichlorophenoxyacetic acid (2,4-D) and organophosphate insecticides (16). However, a pooled analysis by De Roos et al. (18) of data from these studies found statistically significantly increased odds ratios (ORs) for NHL with atrazine exposure in combination with exposure to one of three other pesticides (diazinon, alachlor, or dicamba). A case-control study of ovarian cancer found an increased risk among women farmers "possibly" and "definitely" exposed to atrazine in their occupation (19). Ecologic studies have shown increased risks of stomach (20), prostate, brain, testicular (21), and breast cancers (22) and leukemia and decreased risks of colon (20) and breast cancers (23) with increasing amounts of triazine herbicides applied or with increasing levels measured in drinking water.

Based on inadequate data for humans and limited data for experimental animals, atrazine was classified as "possibly carcinogenic to humans" (Group 2B) by the International Agency for Research on Cancer in 1999 (24). The EPA has classified atrazine as "not likely to be a human carcinogen" (25). However, the limited data on the effects of atrazine among humans, the provocative findings in animal studies, and the frequency with which this herbicide is used warrant further investigation among exposed populations. We therefore investigated site-specific cancer incidence and risk among pesticide applicators exposed to atrazine in the Agricultural Health Study cohort using a longer follow-up period and a larger number of case patients than the prostate cancer analysis by Alavanja et al. (10).

SUBJECTS AND METHODS

Cohort Enrollment and Follow-up

The Agricultural Health Study cohort is a prospective study of 57 311 private and commercial applicators licensed to apply restricted-use pesticides who live in Iowa or North Carolina and who were recruited between 1993 and 1997 (26). Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and the National Death Index to ascertain vital status. Incident cancers were identified for the time period from the date of enrollment through December 31, 2001, and were coded according to the International Classification of Diseases for Oncology, 2nd edition (ICD-O-2). Cohort members who were alive but no longer residing in Iowa or North Carolina were identified through current address records of the Internal Revenue Service (address information only), Motor Vehicle Registration offices, and pesticide license registries of the state agricultural departments. Person-year accumulation for cancer incidence of individuals who had moved from the state was censored in the year they departed, although they were still followed up for mortality. The mean time of follow-up was 6.5 years. All participants provided verbal informed consent, and the protocol was approved by the institutional review boards of the National Cancer Institute, Batelle, the University of Iowa, and Westat.

Exposure Assessment

A self-administered enrollment questionnaire collected comprehensive exposure data on 22 pesticides and informa-

tion on ever/never use for 28 more pesticides, use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, smoking history, alcohol consumption, cancer history of first-degree relatives, and basic demographics (27). Applicators who completed this questionnaire were also given a self-administered take-home questionnaire, which sought additional information on occupational exposures. The questionnaires may be accessed at <http://www.aghealth.org/questionnaires.html>.

Data from questionnaires completed at enrollment and measurement data from the pesticide exposure literature were used to calculate estimated intensity of exposure to each pesticide using the following algorithm: intensity level = ([mixing status + application method + equipment repair status] × personal protective equipment use) (28).

The scores assigned to each factor in the intensity-level algorithm were not assigned as nominal or ordinal values but were weighted to reflect intensity of exposure as described in the literature. Mixing status (mix) was a three-level variable based on never mixing, personally mixing less than 50% of the time, and personally mixing more than 50% of the time (mix = 0, 3, and 9, respectively). Application method (applic) was a six-level variable based on never applying, use of aerial-aircraft or distribution of tablets, application in furrow, use of boom on tractor, use of backpack, and use of hand spray (applic = 0, 1, 2, 3, 8, 9, respectively). Equipment repair status (repair) was a two-level variable based on not repairing or repairing (repair = 0, 2, respectively). Personal protective equipment use was an eight-level variable based on type of personal protective equipment used while applying pesticides (28).

We constructed two lifetime atrazine exposure metrics for this analysis, each categorized into quartiles, based on the quartile levels among all cancer cases: 1) lifetime days of exposure, based on the product of the midpoints of the questionnaire categories of number of years an applicator personally applied or mixed atrazine and number of days in an average year an applicator personally mixed or applied atrazine (i.e., years of use × number of days used per year, resulting in the following quartiles: ≤19.9, 20.0–56.0, 56.1–178.5, ≥178.5) and 2) intensity-weighted lifetime days of exposure, which was the product of lifetime days of exposure and intensity level (i.e., years of use × number of days used per year × intensity level, resulting in the following quartiles: ≤101.9, 102.0–326.7, 326.8–911.4, ≥911.4).

Statistical Analysis

Prevalent cancer case patients identified at or prior to the time of enrollment (n = 1074) and applicators who did not provide information on atrazine use (n = 2294) were excluded from this analysis, leaving 53 943 applicators. Analyses of first primary incident cancer case patients enabled us to obtain exposure data from each case patient prior to the onset of cancer.

To examine internal exposure-response relationships among participants who reported having ever used atrazine, Poisson regression analyses were carried out for individual cancer sites to estimate rate ratios (RRs) and 95% confidence intervals (CIs) associated with quartiles of lifetime days of exposure (RR_{LD}) or intensity-weighted lifetime days of exposure (RR_{IWLD}), using the lowest quartile as the referent. We investigated only cancer sites for which there were at least 20 case patients with atrazine

exposure. *P* values for trend were calculated using atrazine exposure as a continuous variable, and all statistical tests were two-sided. Rate ratios were adjusted for age at enrollment (as a continuous variable), sex, educational level (high school/GED or lower, beyond high school), alcohol consumption (ever/never), family history of cancer in first-degree relatives (yes/no), state of residence (Iowa/North Carolina), and cigarette smoking history (never/low/high: the median value of pack-years [11.25] among smokers was used to classify low and high categories of smokers). In addition, we carried out the same Poisson analyses described above and included second primary incident cancers as case patients (i.e., both first and second primary cancer case patients were included) to increase the numbers of case patients. Variation ranged from one additional case patient with esophageal cancer and leukemia to 28 additional case patients with prostate cancer.

To ensure the use of the most appropriate reference group—either applicators never exposed to atrazine or applicators exposed to atrazine in the lowest exposure quartile—we carried out a comparison of baseline characteristics between different types of pesticide applicators: 1) applicators never exposed to atrazine, 2) applicators with atrazine exposure in the lowest quartile of lifetime days of exposure, and 3) applicators with atrazine exposure in the highest three quartiles of lifetime days of exposure. We postulated that applicators with baseline characteristics similar to those of the applicators in the highest exposure group would be most appropriate as a reference group for the Poisson regression analyses. Too much difference with respect to these baseline characteristics might introduce residual confounding from a variety of unidentified sources.

Potential confounding from exposure to other pesticides was controlled by adjusting exposure to 10 other pesticides (dicamba, cyanazine, alachlor, trifluralin, 2,4-D, chlorimuronethyl, metribuzine, butylate, phorate, and heptachlor). These pesticides were identified as the 10 most strongly correlated with atrazine out of 50 pesticides measured in the Agricultural Health Study, based on either strength of the correlation coefficient for intensity-weighted lifetime days of exposure (highest: $r = .78$; lowest: $r = .58$) or strength of association for ever/never comparison between atrazine and each of the 28 pesticides in the Agricultural Health Study for which there is ever/never data only. None of the pesticides we evaluated was negatively correlated with atrazine. In the final models, exposure levels of dicamba, cyanazine, alachlor, trifluralin, and 2,4-D were categorized as never, low, and high. The low and high group of each pesticide was classified by the median intensity-weighted exposure-days of each pesticide. For the pesticides chlorimuronethyl, metribuzine, butylate, phorate, and heptachlor, we had information only on ever/never use, so these five were categorized as such.

RESULTS

Selected characteristics of the atrazine exposed (lowest quartile and combined highest three quartiles) and nonexposed applicators in the Agricultural Health Study cohort are presented in Table 1. Among 53 943 subjects with complete exposure information, 36 513 (68%) reported ever having used atrazine, and they contributed a total of 237 045 person-years to the analysis. The cohort, both exposed and nonexposed, comprised primarily white, male, private applicators with relatively low smoking

rates; in both the exposed and nonexposed groups, about half the subjects reported that they had never smoked. Exposed and nonexposed subjects were similar with respect to age, smoking history, alcohol consumption, educational level, and family history of cancer in a first-degree relative. The group consisting of the lowest exposed quartile is observed to be more similar to the group comprising the highest three quartiles than is the nonexposed group on a number of important variables. These include applicator status (i.e., private/commercial), state of residence, involvement in corn production, and use of the 10 pesticides most highly correlated with atrazine. Because of these similarities, we determined that the most appropriate reference group for the exposure-response analyses was applicators in the lowest quartile of atrazine exposure. However, to ensure that we did not overlook any potential associations and to verify our findings, we also carried out exposure-response analyses using the nonexposed applicators as the reference group (data not shown).

The Poisson regression rate ratios of selected cancers for which there were at least 20 atrazine-exposed case patients are presented in Table 2. For all cancers combined, there was no statistically significantly increased risk with increasing quartiles of lifetime days of exposure to atrazine or intensity-weighted lifetime days of exposure. Prostate cancer was the most frequent cancer in the cohort ($n = 554$); we did not detect any increased risk for prostate cancer with increasing atrazine exposure, whether assessed using lifetime days of exposure (highest quartile: $RR = 0.88$, 95% $CI = 0.63$ to 1.23 ; $P_{\text{trend}} = .26$) or intensity-weighted lifetime days of exposure (highest quartile: $RR = 0.89$, 95% $CI = 0.63$ to 1.25 ; $P_{\text{trend}} = .35$), even in subjects exposed for more than 178.5 days. We detected a statistically nonsignificant increased risk for lung cancer with increasing quartiles of lifetime days of exposure (highest quartile: $RR_{LD} = 1.91$, 95% $CI = 0.93$ to 3.94 ; $P_{\text{trend}} = .08$). The risk of lung cancer with intensity-weighted lifetime days of exposure, however, was less consistent across quartiles and diminished somewhat compared with that of lifetime days of exposure in the highest exposure quartile ($RR_{IWL D} = 1.37$, 95% $CI = 0.65$ to 2.86). Further analyses among never smokers, former smokers, and current smokers showed that the rate ratios of lung cancer were increased only in former smokers. However, we did not detect a statistically significant interaction between atrazine exposure and smoking history with respect to lung cancer. For bladder cancer, we also found no association between risk and exposure. A statistically nonsignificantly increased risk was observed with lifetime days of exposure (highest quartile: $RR_{LD} = 3.06$, 95% $CI = 0.86$ to 10.81 ; $P_{\text{trend}} = .18$) but not with intensity-weighted lifetime days of exposure (highest quartile: $RR_{IWL D} = 0.85$, 95% $CI = 0.24$ to 2.94). Elevated risks were suggested for NHL for both the analysis using lifetime days of exposure and the analysis using intensity-weighted lifetime days of exposure (highest quartile: $RR_{LD} = 1.61$, 95% $CI = 0.62$ to 4.16 , $P_{\text{trend}} = .35$; highest quartile: $RR_{IWL D} = 1.75$, 95% $CI = 0.73$ to 4.20 , $P_{\text{trend}} = .14$) and multiple myeloma (highest quartile: $RR_{LD} = 1.60$, 95% $CI = 0.37$ to 7.01 , $P_{\text{trend}} = .41$; highest quartile: $RR_{IWL D} = 2.17$, 95% $CI = 0.45$ to 10.32 , $P_{\text{trend}} = .21$). However, the numbers of applicators with NHL ($n = 68$) and multiple myeloma ($n = 23$) were small, RR estimates were not statistically significant, and there were no indications of a linear dose-response trend. We found no evidence of increased risks for cancers of the oral cavity, colon, rectum, pancreas, or kidney or for melanoma or leukemia.

Table 1. Selected characteristics of applicators by atrazine exposure in the Agricultural Health Study based on 1993–1997 enrollment data

Characteristics	Nonexposed group, No. (%) (n = 17 430)	Lowest exposed quartile, No. (%) (n = 9566)*	Highest three quartiles combined, No. (%) (n = 26 947)†
Age, y			
<40	6741 (38.7)	3012 (31.5)	7906 (29.3)
40–49	4064 (23.3)	2761 (28.9)	8191 (30.4)
50–59	3121 (17.9)	1933 (20.2)	6038 (22.4)
≥60	3504 (20.1)	1859 (19.4)	4811 (17.9)
Sex			
Male	16 272 (93.4)	9439 (98.7)	26 759 (99.3)
Female	1158 (6.6)	127 (1.3)	188 (0.7)
State of residence			
Iowa	8684 (49.8)	6787 (71.0)	19 875 (73.8)
North Carolina	8746 (50.2)	2779 (29.0)	7072 (26.2)
Applicator type‡			
Private	15 010 (86.1)	9208 (96.3)	24 952 (92.6)
Commercial	2420 (13.9)	358 (3.7)	1995 (7.4)
Smoking history			
Never	8671 (49.7)	5244 (54.8)	14 523 (53.9)
Low (<11.25 pack-years)	3941 (22.6)	2050 (21.4)	5815 (21.6)
High (≥11.25 pack-years)	4135 (23.7)	2005 (21.0)	5847 (21.7)
Missing	683 (4.0)	267 (2.8)	762 (2.8)
Alcohol consumption			
No	6267 (36.0)	2847 (29.8)	7415 (27.5)
Yes	10 113 (58.0)	6318 (66.0)	18 740 (69.5)
Missing	1050 (6.0)	401 (4.2)	792 (3.0)
Educational level			
High school/GED or lower	9722 (55.8)	5348 (55.9)	14 934 (55.4)
Beyond high school	7254 (41.6)	4037 (42.2)	11 505 (42.7)
Missing	454 (2.6)	181 (1.9)	508 (1.9)
Family history of cancer in first-degree relatives			
No	9812 (56.3)	5140 (53.7)	14 369 (53.3)
Yes	5521 (31.7)	3554 (37.2)	10 491 (38.9)
Missing	2097 (12.0)	872 (9.1)	2087 (7.8)
Corn production			
No	9764 (56.0)	2293 (24.0)	4879 (18.1)
Yes	7666 (44.0)	7273 (76.0)	22 068 (81.9)
Ever exposure to 10 pesticides most highly correlated with atrazine			
Dicamba	3713 (23.6)§	4940 (56.5)	16 246 (63.9)¶
Cyanazine	1636 (10.4)§	3686 (42)	15 258 (59.6)¶
Alachlor	3452 (22.1)§	4815 (54.7)	17 872 (69.5)¶
Trifluralin	4055 (26.1)§	5030 (57.0)	16 989 (66.2)¶
2,4-Dichlorophenoxyacetic acid	8954 (52.1)§	7586 (80.0)	23 160 (86.5)¶
Chlorimuronethyl	2538 (16.7)§	3010 (34.6)	13 144 (52.1)¶
Metribuzin	2540 (16.7)§	3901 (44.8)	15 528 (61.5)¶
Butylate	1328 (8.8)§	2295 (26.5)	11 896 (47.3)¶
Phorate	2091 (13.8)§	2714 (31.2)	10 783 (42.9)¶
Heptachlor	847 (5.6)§	1113 (12.9)	5201 (20.9)¶

*First quartile of lifetime days of exposure (years of use × days of use per year).

†Second, third, and fourth quartiles of lifetime days of exposure (years of use × days of use per year).

‡“Private applicators” refers primarily to individual farmers and “commercial” refers to professional pesticide applicators.

§Ever exposed to indicated chemical but not to atrazine (thus, numbers in columns do not sum to 100%).

||Ever exposed to indicated chemical and in lowest quartile of atrazine exposure (thus, numbers in columns do not sum to 100%).

¶Ever exposed to indicated chemical and in the highest three quartiles of atrazine exposure (thus, numbers in columns do not sum to 100%).

Cancer risk patterns were similar when we used never exposed applicators as the reference group, making comparisons for each of the four quartiles of atrazine exposure (data not shown). For prostate cancer, there was no increased risk, whether we used lifetime days of exposure (Q1, $RR_{LD} = 0.98$; Q2, $RR_{LD} = 0.87$; Q3, $RR_{LD} = 0.74$; Q4, $RR_{LD} = 0.83$; $P_{trend} = .09$) or intensity-weighted lifetime days of exposure (Q1, $RR_{IWL D} = 0.91$; Q2, $RR_{IWL D} = 0.94$; Q3, $RR_{IWL D} = 0.78$; Q4, $RR_{IWL D} = 0.79$; $P_{trend} = .11$). For both lung and bladder cancers, there were statistically nonsignificantly elevated rate ratios only for the highest quartile of lifetime days of exposure; again, for intensity-weighted lifetime days of

exposure, the effect was diminished in the highest quartile. For NHL, there was a steadily increasing, statistically nonsignificant linear trend for quartiles of both exposure metrics (highest quartile: $RR_{LD} = 2.16$, 95% CI = 0.84 to 5.59, $P_{trend} = .06$; highest quartile: $RR_{IWL D} = 2.78$, 95% CI = 1.16 to 6.68, $P_{trend} = .02$). For multiple myeloma, there was a similar pattern for both metrics (highest quartile: $RR_{LD} = 4.75$, 95% CI = 0.68 to 33.08, $P_{trend} = .14$; highest quartile: $RR_{IWL D} = 4.71$, 95% CI = 0.72 to 30.69, $P_{trend} = .07$). For all other cancers investigated, no associations were found when applicators never exposed to atrazine were used as the comparison group.

Table 2. Rate ratios (RRs) and 95% confidence intervals (CIs) from Poisson regressions for selected cancers* by lifetime days of exposure and intensity-weighted days of exposure to atrazine† among Agricultural Health Study cohort applicators

Cancer site	Exposure days (quartiles)‡	Exposure to atrazine					
		N§	RR _{LD} (95% CI)	<i>P</i> _{trend} ¶	N§	RR _{IWLD} (95% CI)#	<i>P</i> _{trend} ¶
All cancers	1-20	1361			1355		
	21-56	357	1.00 (referent)		340	1.00 (referent)	
	57-178.5	348	1.05 (0.87 to 1.27)		338	0.97 (0.80 to 1.18)	
	>178.5	358	0.90 (0.74 to 1.11)	.68	338	0.96 (0.79 to 1.18)	.28
Oral cavity	1-20	298	1.01 (0.82 to 1.26)		339	0.88 (0.71 to 1.11)	
	21-56	38			38		
	57-178.5	9	1.00 (referent)		12	1.00 (referent)	
	>178.5	19	1.93 (0.71 to 5.25)		10	0.74 (0.25 to 2.16)	
Esophagus	1-20	5	0.69 (0.20 to 2.38)	.18	10	0.86 (0.30 to 2.47)	.20
	21-56	5	0.50 (0.11 to 2.24)		6	0.36 (0.10 to 1.38)	
	57-178.5	20			20		
	>178.5	4	1.00 (referent)		3	1.00 (referent)	
Colon	1-20	8	1.69 (0.39 to 7.28)		8	5.57 (0.63 to 49.05)	
	21-56	7	0.77 (0.14 to 4.23)	.27	6	3.03 (0.29 to 31.62)	.77
	57-178.5	1	0.29 (0.03 to 3.35)		3	2.70 (0.23 to 31.21)	
	>178.5	110			108		
Rectum	1-20	28	1.00 (referent)		30	1.00 (referent)	
	21-56	22	0.79 (0.40 to 1.57)	.98	24	0.65 (0.33 to 1.28)	.64
	57-178.5	35	1.12 (0.59 to 2.10)		21	0.61 (0.30 to 1.25)	
	>178.5	25	0.88 (0.41 to 1.89)		33	0.86 (0.43 to 1.73)	
Pancreas	1-20	52			52		
	21-56	11	1.00 (referent)		12	1.00 (referent)	
	57-178.5	8	1.11 (0.41 to 3.00)	.65	8	0.79 (0.29 to 2.16)	.79
	>178.5	17	0.97 (0.35 to 2.69)		14	0.88 (0.32 to 2.42)	
Lung	1-20	16	1.38 (0.47 to 4.02)		18	0.84 (0.29 to 2.44)	
	21-56	21			21		
	57-178.5	4	1.00 (referent)	.97	4	1.00 (referent)	.42
	>178.5	9	1.26 (0.27 to 5.84)		9	0.96 (0.23 to 4.00)	
Lung	1-20	5	1.14 (0.24 to 5.49)		5	0.57 (0.11 to 2.90)	
	21-56	3	1.13 (0.19 to 6.61)	.97	3	0.56 (0.10 to 3.10)	.42
	57-178.5	118			117		
	>178.5	27	1.00 (referent)		27	1.00 (referent)	
Melanoma	1-20	25	0.87 (0.40 to 1.87)	.08	19	0.69 (0.30 to 1.57)	.19
	21-56	37	1.13 (0.56 to 2.29)		37	1.56 (0.78 to 3.14)	
	57-178.5	29	1.91 (0.93 to 3.94)		34	1.37 (0.65 to 2.86)	
	>178.5	52			52		
Prostate	1-20	12	1.00 (referent)	.84	14	1.00 (referent)	.36
	21-56	12	1.06 (0.44 to 2.56)		10	0.57 (0.22 to 1.46)	
	57-178.5	13	1.18 (0.50 to 2.79)		17	1.31 (0.59 to 2.92)	
	>178.5	15	1.05 (0.39 to 2.84)		11	0.41 (0.14 to 1.20)	
Bladder	1-20	554			552		
	21-56	160	1.00 (referent)	.26	143	1.00 (referent)	.35
	57-178.5	135	0.89 (0.66 to 1.21)		143	1.03 (0.76 to 1.41)	
	>178.5	143	0.75 (0.56 to 1.03)		132	0.86 (0.62 to 1.20)	
Kidney	1-20	116	0.88 (0.63 to 1.23)		134	0.89 (0.63 to 1.25)	
	21-56	47			47		
	57-178.5	10	1.00 (referent)	.18	10	1.00 (referent)	.71
	>178.5	12	2.25 (0.67 to 7.62)		14	1.21 (0.39 to 3.74)	
Non-Hodgkin lymphoma	1-20	9	1.04 (0.27 to 4.05)		12	1.01 (0.31 to 3.29)	
	21-56	16	3.06 (0.86 to 10.81)		11	0.85 (0.24 to 2.94)	
	57-178.5	40			40		
	>178.5	12	1.00 (referent)	.22	13	1.00 (referent)	.27
Multiple myeloma	1-20	8	0.78 (0.27 to 2.33)		8	0.10 (0.01 to 0.83)	
	21-56	11	0.33 (0.08 to 1.32)		8	0.50 (0.15 to 1.63)	
	57-178.5	9	0.58 (0.15 to 2.25)		11	0.43 (0.12 to 1.54)	
	>178.5	68			68		
Multiple myeloma	1-20	17	1.00 (referent)	.35	17	1.00 (referent)	.14
	21-56	19	1.56 (0.66 to 3.69)		16	0.88 (0.35 to 2.27)	
	57-178.5	17	1.59 (0.67 to 3.79)		15	1.36 (0.56 to 3.28)	
	>178.5	15	1.61 (0.62 to 4.16)		20	1.75 (0.73 to 4.20)	
Multiple myeloma	1-20	23			23		
	21-56	7	1.00 (referent)	.41	6	1.00 (referent)	.21
	57-178.5	4	0.57 (0.10 to 3.13)		2	0.71 (0.12 to 4.30)	
	>178.5	5	1.19 (0.31 to 4.65)		7	1.85 (0.42 to 8.24)	
Multiple myeloma	1-20	7	1.60 (0.37 to 7.01)		8	2.17 (0.45 to 10.32)	
	21-56	4	0.57 (0.10 to 3.13)		2	0.71 (0.12 to 4.30)	
	57-178.5	5	1.19 (0.31 to 4.65)		7	1.85 (0.42 to 8.24)	
	>178.5	7	1.60 (0.37 to 7.01)		8	2.17 (0.45 to 10.32)	

(Tables continues)

Table 2 (continued).

Cancer site	Exposure days (quartiles)‡	Exposure to atrazine					
		N§	RR _{LD} (95% CI)	P _{trend} ¶	N§	RR _{IWLD} (95% CI)#	P _{trend} ¶
Leukemia		41			40		
	1-20	9	1.00 (referent)		7	1.00 (referent)	
	21-56	12	1.04 (0.39 to 2.74)		16	1.64 (0.63 to 4.25)	
	57-178.5	10	0.61 (0.21 to 1.78)		6	0.41 (0.11 to 1.49)	
	>178.5	10	0.57 (0.17 to 1.91)	.22	11	0.56 (0.17 to 1.86)	.11

*Cancers for which there were at least 20 exposed case patients or an *a priori* hypothesis about an association with atrazine. Rate ratio adjusted for age, sex, alcohol consumption, residence on a farm, smoking status, educational level, family history of cancer, state of residence, and use of 10 most highly correlated pesticides with atrazine.

†Total number exposed to atrazine = 36 513.

‡Quartiles for lifetime days of exposure. Units for intensity-weighted lifetime days of exposure are not displayed in this table because they do not have an intrinsic value.

§Number of cancer-specific case patients exposed to atrazine (total and for each quartile of exposure).

||RR_{LD} = rate ratio of lifetime days of exposure (i.e., years of use × number of days of use per year).

¶P values were two-sided.

#RR_{IWLD} = rate ratio of intensity-weighted lifetime days of exposure (i.e., years of use × number of days of use per year × intensity index).

We carried out the same Poisson analyses described above and included second primary incident cancers as case patients (i.e., both first and second primary cancer case patients included; data not shown) to increase the numbers of case patients. Variation ranged from one additional case patient with esophageal cancer and leukemia to 28 additional case patients with prostate cancer. The results did not differ substantially from those presented in Table 2.

DISCUSSION

We found no associations between cancer incidence and atrazine exposure, whether atrazine was analyzed as a cumulative measure (lifetime days of exposure) or as an intensity-weighted cumulative measure (intensity-weighted lifetime days of exposure). Although rate ratios for NHL, multiple myeloma, lung cancer, and bladder cancer increased with both lifetime days and intensity-weighted lifetime days of atrazine exposure, confidence intervals were wide, and tests for trend were not statistically significant. Similar results were seen whether we used applicators in the lowest exposed quartile or applicators never exposed to atrazine as the reference group.

A recent study of cancer incidence among triazine herbicide manufacturing workers in a plant in Louisiana found a statistically significant excess of prostate cancer for actively working company employees (excluding contract or inactive company employees), compared with the general population in that region (SIR = 394, 95% CI = 128 to 902) (8). However, the high observed incidence of prostate cancer in the Louisiana plant workers may have been due to the frequent PSA testing of these employees, 98% of whom had at least one PSA test before the age of 45. Of the 11 cases, nine were diagnosed at an early clinical stage. In our study, there was considerable power to investigate risk of prostate cancer (1-β = 0.89 to detect a rate ratio of 1.3 in the highest quartile, assuming a trend over all quartiles) with atrazine exposure, and we found no increased risk, even for those who had applied atrazine for more than 178.5 days (the highest quartile of exposure) or had the highest intensity-weighted lifetime days of exposure.

Our data suggest no clear association between NHL and multiple myeloma incidence and atrazine exposure. However, we did see some evidence of such an association, and further

follow-up is needed to determine whether such an association exists. The only other prospective study on cancer and atrazine is from a cohort of triazine herbicide manufacturing workers, in which there were increased standardized incidence ratios for all lymphatic and hematopoietic cancers (n = 7, 4.4 expected), NHL (n = 3, 2.3 expected), and multiple myeloma (n = 2, 0.4 expected) among a group of men with “definite” or “probable” exposure (8). A mortality study based on the same population detected increased standardized mortality ratios for NHL (n = 4, 1.1 expected); however, the data did not have statistical power to show trends in rates by years worked and years since hire (9). Increased risk of NHL in men was associated with atrazine use after adjustment for other commonly used pesticides in a pooled analysis of the NCI-sponsored case-control studies conducted in Nebraska, Kansas, and Iowa/Minnesota (18). This study also found some evidence of a possible interaction between exposure to atrazine and other pesticides and the risk of NHL. The number of NHL cases in the Agricultural Health Study cohort is too small to provide the statistical power to attempt such an analysis at the present time. In an analysis of NHL by presence or absence of the t(14;18) chromosomal translocation, a statistically significant increased risk was associated with atrazine exposure for patients with the translocation, but not among those lacking it (29), suggesting that further refinement of case definition in future studies may be worthwhile. A previous case-control study observed a weak association between atrazine exposure and multiple myeloma incidence (OR = 1.3, 95% CI not reported) (13), whereas another study found no association (OR = 0.8, 95% CI = 0.4 to 1.6) between multiple myeloma and mixing, handling, or applying atrazine (30).

Slight suggestions of increased risk were found for lung and bladder cancer in the highest quartile of lifetime days of exposure to atrazine. However, the rate ratios in the intensity-weighted lifetime days of exposure analyses were weak for lung cancer and essentially null for bladder cancer. We also found similar patterns using the never exposed applicators as a reference group. Because the respiratory system may be an important route of exposure for lung cancer, use of the intensity algorithm, which weighs dermal exposure more heavily, may have increased measurement error. We further investigated the relationship between lung cancer and atrazine by stratifying the popu-

lation into never smokers, former smokers, and current smokers. That the rate ratios were highest among former smokers and null among current smokers suggests that our findings of a slight increase in risk may not be attributable solely to smoking. To our knowledge, there are no *a priori* hypotheses for an association between atrazine exposure and lung cancer. However, atrazine was found in lung tissue at autopsy of a suicide victim poisoned by ingestion of an herbicide mix containing atrazine (31). The lung was one of the organs that showed the highest concentrations of atrazine. The inconsistencies between the two analyses for bladder cancer leave us doubtful. We will continue to follow up both cancers with respect to atrazine exposure.

The toxicologic activity of atrazine in humans is unclear. Toxicity studies have examined various endpoints from atrazine exposure, including carcinogenicity, genotoxicity, endocrine disruption, and immunotoxicity. The majority of animal studies indicate that atrazine has low genotoxicity, but there has been no study of genotoxicity in humans. In male and female rats, atrazine disrupts hypothalamic stimulation of pituitary function, resulting in attenuation of luteinizing hormone levels (24). This mechanism results in increased rates of mammary tumors in some strains of female rats. In male rats, atrazine causes decreased production of testosterone by Leydig cells (32) and reduced seminal vesicle and prostate weights (32). However, the potential for endocrine disruption in humans from atrazine exposure and its implications for carcinogenesis are not known. Several studies have observed immunotoxicity of atrazine in animals *in vivo* and in human and animal cells *in vitro*; however, the evidence to date has not established the immune system as a target for atrazine toxicity. Two studies in rodents showed that atrazine exposure decreased levels of circulating lymphocytes, although several other immune parameters were unchanged (33,34). Several recent studies have observed impaired immune function associated with administration of atrazine to cells *in vitro*, including impaired cytokine production (interferon γ , interleukin 5, and tumor necrosis factor- α) by human peripheral blood mononuclear cells (35) and decreased ability of human natural killer cells to lyse tumor cells (36). Immunotoxicity may be particularly relevant for lymphohematopoietic cancers.

The Agricultural Health Study has several important strengths. It is the largest study to date of pesticide applicators exposed to atrazine. Exposure information was gathered prior to cancer diagnosis, thereby minimizing recall bias. In general, farmers provide reliable information and considerable detail regarding their pesticide application history (37–40). The Agricultural Health Study cohort consists of licensed pesticide applicators who are responsible for thoroughly understanding pesticide regulations and for purchasing and applying chemicals on their farms (41). Recall of pesticide use by the Agricultural Health Study cohort has been shown to be consistent with the dates these pesticides came on the market (41). To our knowledge, this is the first human study of atrazine to use a semiquantitative method to assess exposure; comprehensive questionnaire data were used to quantify atrazine exposure levels, providing greater discrimination between high and low exposures than previous studies that broadly defined exposure as “ever used” atrazine. In addition, detailed information on the use of many common pesticides and lifestyle characteristics allowed us to adjust for potential confounding factors.

Certain limitations of our data reduce the number and kinds of inferences we can make regarding atrazine and its association

with specific cancers. Although the Agricultural Health Study cohort is large and many participants reported atrazine use, the small number of selected cancers occurring during the 6.5-year average follow-up period prevented estimation of precise effects. In addition, most atrazine applicators were male (99%), precluding our ability to assess the association between atrazine exposure and female cancers, including ovarian and breast cancers, which have been associated with exposure to triazine herbicides (19,22). Our analysis provides limited information on the timing of pesticide use in relation to disease. Additionally, with only 6.5 years of follow-up, our ability to make conclusions concerning latency and secular changes in personal protective equipment is limited. We will be able to better address these issues with a longer follow-up period and more exposure data from subsequent phases of the study. Finally, there are hypotheses concerning gestation and early childhood as periods sensitive to endocrine disruptors (42), and because our study focused on adult exposures, we cannot address the risk associated with exposures in early life. Although our study used more detailed exposure estimates than did earlier studies, estimates for lifetime days of exposure and intensity-weighted lifetime days of exposure, as well as measures of confounding, include error that could bias our results toward the null. For example, there is some variation we could not account for with respect to the categorical attainment of days exposed in each year. Another source of variation is the number of hours worked in a day of pesticide application. Later phases of the Agricultural Health Study will address these exposure variables and will provide a more precise estimate of exposure.

Despite the limitations noted above, our prospective study of cancer incidence among atrazine exposed pesticide applicators provided an opportunity afforded in few other studies to evaluate cancer risks associated with exposure to atrazine, while adjusting for other common pesticide exposures and lifestyle factors. No increased risk of prostate cancer was observed among 554 atrazine exposed cases with increasing exposure to atrazine, even among those with more than 178.5 days of lifetime use. Statistical power was limited for some cancers, but certain intriguing suggestions of association were observed for non-Hodgkin lymphoma, multiple myeloma, lung cancer, and bladder cancer, which we intend to monitor and further investigate as more cases develop in this cohort.

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NOTE

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**Review of “Cancer Incidence Among Pesticide
Applicators Exposed to Atrazine in the
Agricultural Health Study”**

Rusiecki JA et al.

*Submitted by Jack Mandel, Ph.D., M.P.H.
Rollins Professor and Chair
Department of Epidemiology
Rollins School of Public Health
Emory University*

November 20, 2004

Some Background on the Agricultural Health Study

The Agricultural Health Study, a prospective cohort study in North Carolina (NC) and Iowa, is designed to: 1) identify and quantify cancer risks associated with exposure to pesticides and other agricultural agents, 2) evaluate a number of noncancer health risks such as reproductive effects, neurobehavioral outcomes, immunologic effects and others, 3) evaluate a variety of disease risks among spouses and children of farmers that may be associated with both direct and indirect contact to pesticides and other agricultural chemicals, 4) assess current and past occupational and nonoccupational exposures through interviews and environmental and biologic monitoring, 5) study the relationship between agricultural exposures, exposure biomarkers, biologic outcomes, and genetic susceptibility factors related to carcinogenesis and 6) identify and quantify cancer and other disease risks associated with a variety of lifestyle factors (Alavanja et al. 1996). The initial goal was to develop a cohort of 112,000 adult study subjects including 42,000 women (Alavanja et al. 1994). This goal was subsequently modified to include approximately 75,000 adult subjects perhaps reflecting the difficulty in recruiting the desired number of participants (Alavanja et al. 1996). The issue of potential selection bias was partially addressed by Tarone et al. who evaluated compliers and noncompliers early in the recruitment phase of the trial (Tarone et al. 1997). They noted some differences, namely, the increased age of responders and subsequent higher cumulative farm exposures and slightly lower current farm exposures than the base population of all farmer applicators. Herbicides in general, and atrazine in particular, were somewhat more likely to be applied by participants than nonparticipants. Participants in both states reported more cancers and more cancers in family members than nonparticipants, although neither of these differences was statistically significant.

In a subsequent paper the Agricultural Health Study team evaluated the reliability of self-reported information on pesticide use and demographic and lifestyle factors by obtaining a second questionnaire one year later from about 4,000 Iowa farmers enrolled in the study (Blair et al. 2002). The percentage of participants providing the same answer on both questionnaires was above 80% for ever/never use of specific pesticides but was

considerably lower for other more specific variables such as years mixed or applied pesticides (55%), days per year pesticides mixed or applied (45%), number of years atrazine was mixed or applied (50%), and the decade in which atrazine was first applied (64%). Thus, there is the potential for considerable error in the self reports of specific pesticides and their frequency of use. This would suggest that attention must be paid to the validity of the data in drawing conclusions about associations with disease endpoints.

The Study by Rusiecki et al

The study by Rusiecki et al. provides results from a self-administered questionnaire completed at the time of enrollment (1993-7) by 57,311 private and commercial applicators licensed to apply restricted-use pesticides in Iowa and North Carolina (Rusecki et al. 2004). Members of this cohort were matched to cancer registries and death certificate registries in the two states and to the National Death Index to ascertain both incident cancer cases and deaths from cancer. Follow-up of individuals who left the state was censored in year of departure for incidence. Vital status was determined through the end of 2001. Mean follow-up time was 6.5 years.

Exposure was assessed by a self-administered questionnaire that requested detailed information on 22 pesticides and ever/never use for 28 more pesticides along with data on demographic characteristics, use of personal protective equipment, methods of applying pesticides, pesticide mixing techniques, equipment repair, smoking history, alcohol consumption, and cancer history of first degree relatives. A second take home questionnaire to obtain more detailed occupational information was offered to those who completed the initial questionnaire. Data from the initial questionnaire and “measurement data from the pesticide exposure literature were used to calculated estimated intensity of exposure to each pesticide using an algorithm published by Dosemeci et al. (Dosemeci et al. 2002).

The two lifetime atrazine exposure metrics that were used were categorized into quartiles based on the quartile levels of all cancer cases. The development of these exposure metrics largely relied on the self-reported information from study participants. Poisson

regression analysis was the primary method of analysis with adjustment for confounders. Analyses were conducted for all cancer sites with at least 20 cases (n=14), for two exposure matrices and four exposure categories. Table 2 of the paper presents 112 risk ratios (28 are baseline values =1.0). None of these rate ratios is statistically significant although by chance about 4 would have been expected. More than fifty percent of the 84 rate ratios were below 1.0. Tests for trend (“dose-response”) were done for all 28 comparisons and none was statistically significant. In fact, a number of additional risk ratios were computed including an analysis using never exposed applicators as the reference group (complete data not presented in the paper) and analyses for some specific cancers (eg lung) by specific risk factors (eg smoking). In total, well over 200 risk ratios were computed and only one significant value is cited in the published paper.

The authors appropriately concluded that the study found no association between atrazine and cancer. They stated, “we found no associations between cancer incidence and atrazine exposure, whether atrazine was analyzed as a cumulative measure (lifetime days of exposure) or as an intensity-weighted cumulative measure (intensity-weighted lifetime days of exposure).” In addition, this study corroborated the finding that the increased rate of prostate cancer observed at the Syngenta plant in Louisiana was due to PSA testing as shown in a subsequent case-control study (McLennan et al. 2002, Hessel et al. 2004). As Rusiecki et al. point out, this study had considerable power to investigate the risk of prostate cancer and the results showed that even for the highest exposure categories, including the highest quartile for intensity-weighted lifetime days of exposure, the risk ratios were less than 1.0.

The authors appropriately concluded that the data “suggest no clear association between NHL and multiple myeloma incidence and atrazine exposure” yet they later state that there is “some evidence of such an association.” This is an unusual conclusion given the results for these cancers in the context of the entire study. All but one of the reported risk ratios (over 200) were not statistically significant. In addition, as shown in prior papers, there is potential for reporting bias with self-reported exposures. In fact, the study by

Blair et al. shows that the reliability for reporting specific exposure information on atrazine is only about 50%, thus there is potential for information bias.

Another concern is selection bias. Although it might be assumed that since exposure information is collected prior to the diagnosis (not prior to disease onset as stated by the authors since this time is not known), selection bias cannot occur. This is not necessarily true, particularly in this case where the farmers and their families knew the focus of the study. Therefore, it is possible that a farmer who uses pesticides and has a family history of cancer might be more inclined to participate in this study than a farmer who is not a heavy user of pesticides and does not have a family history of cancer. In this regard it is interesting to note that participants in the study did report greater use of herbicides than nonparticipants (84.0% v. 79.2% in Iowa and 69.5% v. 65.0% in North Carolina) and greater use of atrazine (32.8% v. 28.3% and 16.2% v. 15.3% in Iowa and North Carolina respectively). In addition, participants in both states reported more cancers in first-degree relatives than nonparticipants (40.0% v. 36.5% and 35.9% v. 30.4%) (Tarone et al. 1997). This does not demonstrate the presence of selection bias but merely suggests that the potential for this is a reasonable assumption.

The only statistically significant finding reported in the paper is for the analysis of NHL using never exposed as the reference group and using the algorithm, intensity-weighted lifetime days of exposure. It was not found for lifetime days of exposure and it was not found in the main analysis using the lowest exposure category as the reference. The algorithm, based on (mixing status + application method + equipment repair status) x personal protective equipment, has never been validated by the authors. In a recent analysis using five day 24-hour urine biomonitoring data from farm families around the time of pesticide application and similar questionnaire data, Acquavella et al. showed that this algorithm may not be valid and that there may be substantial misclassification (Acquavella et al. 2004). They found relatively low correlations between the algorithm and both field observations and self-reported information, although the correlations with field observations were slightly better. In addition, they showed that a generic approach to exposure assessment is not appropriate since the correlations between the algorithm

and specific pesticides were different for each pesticide. They proposed that future efforts to assess retrospective exposure using a derived formula should be specific for different classes of pesticides with similar physical/chemical properties. In addition, there needs to be validation of the data when self-reported information is used and validation of the algorithm that is used.

The results of the study by Rusiecki et al. are essentially null and the authors appropriately conclude there is no association between cancer incidence and atrazine. It is therefore surprising that they end the paper by suggesting that there were “certain intriguing suggestions of association.” This latter statement contradicts their earlier and more appropriate statement that more accurately reflect the findings. Perhaps the authors merely stated the usual caution that one exercises in concluding an epidemiologic study along with the call for continued research.

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

October 21, 2004

MEMORANDUM

SUBJECT: Review of "A Nested Case-Control Study of Prostate Cancer and Atrazine Exposure"
DP Barcode D297437, MRID# 460894-01, Chemical #080803

FROM: Jerome Blondell, Ph.D., Health Statistician
Chemistry and Exposure Branch 1
Health Effects Division (7509C)

THRU: Francis B. Suhre, Senior Scientist
Chemistry and Exposure Branch 1
Health Effects Division (7509C)

TO: Catherine Eiden, Senior Scientist
Reregistration Branch 3
Health Effects Division (7509C)

BACKGROUND

This review considers additional information submitted by Syngenta Crop Protection, Inc. An earlier review (D287278, January 15, 2003) considered the results of a cancer incidence study at this plant. Additional exposure information has been provided in a report transmitted to the Office of Pesticide Programs (OPP) on November 1, 2002 titled "Summary of Information on Potential Atrazine Exposure for 12 out of 17 Prostate Cancer Cases Reported by Delzell et al. 2001" by Charles B. Breckenridge. In addition to this report, OPP also received comments from the Natural Resources Defense Council (NRDC, June 3 and July 30, 2002) and a panel report titled "An Evaluation of the Report by Dr. Delzell et al. on "A Follow-up Study of Cancer Incidence Among Workers in Triazine-Related Operations at the Novartis St. Gabriel plant"" submitted by Hans-Olov Adami, Graham Colditz, Jack Mandel, and Dimitrios Trichopoulos.

The primary purpose of this review is to consider the newly submitted exposure information.

An earlier study by Delzell et al. 2001 found an excess of prostate cancer cases relative to the number of expected cases based on rates calculated using the Louisiana Cancer Registry for the State and for the local industrial corridor where the manufacturing plant resides. The earlier study divided workers into three groups: company employees (n = 757), who were generally full-time and eligible for the prostate specific antigen (PSA) screening program and contract maintenance workers (n = 601) and contract production workers (n = 687) who were not eligible for screening and usually worked for a much shorter duration at the plant. Earlier reviews criticized this study for absence of exposure information that prevented determination of whether prostate cancer cases were also workers experiencing the highest exposure to atrazine.

The number of prostate cancers in contract employees was equal to expectation. This suggests that screening could have been the main factor responsible for increased prostate cancer in plant employees. However, another possible explanation was the relatively short duration of most contract employees at the plant which may have been insufficient to allow prostate cancers to develop. It was hypothesized by reviewers that those workers with the longest duration exposure would be at greatest risk. Therefore, it was proposed to examine exposure in company employees to see if exposure might explain the increased prostate cancer instead of the increased screening for PSA. The registrant agreed to fund an independent study with Health Practice Exponent, Inc. to examine this possibility.

Health Practice Exponent, Inc. designed and conducted a nested case-control study of prostate cancer and atrazine exposure. The cases were the 14 prostate cancers occurring among company employees through 1999. Twelve of the 14 were known to the company and consented to release medical records. Two were identified by the Louisiana Tumor Registry and were not known to the company and their consent could not be obtained. Controls were selected randomly from employees matched by age and race. There were a total of 130 controls such that each case had 10-14 controls with the exception of one older case who had just 3 eligible controls.

Both records of PSA screening and digital rectal exam (DRE) were obtained from all study subjects. Demographic and work data were collected to permit exposure assessment and statistically adjusted comparisons between cases and controls. Work histories consisted of job title, department name, and start and end dates for each job. Work histories were cataloged to date of diagnosis for cases and the same date for controls. Work histories spanned from 1970 when the plant began operation to the latest year of diagnosis which was 1999.

Using work histories, a list of 341 combinations of job title and department was generated without the knowledge of the case or control status among the subjects. The 341 combinations were then placed into one of five categories of exposure by an industrial hygienist and three long-time workers at the plant. These four raters worked independently without knowledge of the subject's case or control status. The five categories of exposure were:

1. No exposure to atrazine during normal work activities;

2. Occasional exposure, but normal activities did not involve exposure;
3. Regular exposure to low levels;
4. Regular exposure to intermediate levels;
5. Regular exposure to high levels.

Three of the four raters agreed on the classification of 255 (75%) of the job/department combinations. The raters met to discuss the classification of the remainder by consensus. Review of worker activities also took into account the decline in exposure over time due to upgraded procedures, automated packaging, and increased environmental controls.

Potential exposures in the plant were measured, primarily in the packaging and production areas, where atrazine exposure was the highest. Total airborne dust, person air sampling for dust were measured from 1970 to 1987. Starting in 1989 measurements specific to atrazine were taken for airborne and personal air levels. In addition, urine levels of atrazine were measured from 1991 through 1999 in both the packaging and production areas. However, large inter-individual variability between urine values and airborne exposure suggested that urine, which was thought to capture 7-10% of total atrazine dose, was not reliable and could not be validated for individuals. It was useful for confirming relative ranking. Difficulties were noted in earlier measurements of total dust which did not necessarily correlate with respirable levels of atrazine. The limited number of concurrent atrazine and total dust measurements prevent strong inferences about exposure during the earlier years. Nevertheless, the relative ranking of jobs was confirmed by later sampling even though the exact magnitude of earlier exposure could not be extrapolated. In particular, personal dust samples, made up of 80-900% atrazine were collected often enough since 1971 to determine relative changes in atrazine exposure over time. Results from various measurements are presented in tabular and graphical form to permit the reader to determine what the potential exposures were and the associated uncertainties.

A numerical index was developed based on the monitoring data to approximate relative exposures during two time periods, 1970-1984 and 1985-1999. High exposure (category 5 above) was estimated to be 20 times greater than low exposure (category 3 above) for the 1970-1984 time period. Low exposure was estimated to be 100 times greater than no exposure (category 1 above) during normal work activities for the same time period. The more recent time period, 1985 -1999, had less difference between categories. For example, the highest category was estimated to have 250 times more exposure than the lowest.

Exposure for each subject was then estimated in three ways: a time-weighted average intensity of exposure; duration of exposure in days; and cumulative exposure defined as the product of intensity and duration, summed over all jobs.

Cases and controls were compared for the intensity of cancer screening and dates of hire and termination. Conditional logistic regression took into account the atrazine exposure variables and age. A cross tabulation showed that cases generally had greater duration and cumulative exposure than controls. However, when subjects were limited to those receiving PSA screening, this difference disappeared. Cases were more than twice as likely (2.25 x) to have PSA screening as controls and 1.66 times more likely to have had a digital rectal exam. The odds ratio for ever/never

having had a PSA test was 8.5 (95% confidence interval 1.7 - 82.2).

Neither average intensity of exposure or cumulative exposure was associated with prostate cancer based upon conditional logistic regression. Duration of exposure was higher among cases than controls with an odds ratio of 1.3 (95% confidence interval 1.06 - 1.66). However, this statistically significant finding disappeared when only subjects receiving PSA screening were included (odds ratio = 0.96 with a 95% confidence interval of 0.71 - 1.30). The authors state “The results demonstrated that the prostate screening program confounded the results of the study of cancer incidence, and when confounding was removed, there was no evidence of a relationship between atrazine exposure and prostate cancer”. The present reviewer agrees with this conclusion. Other supplemental analysis limited subjects to only those with at least 20 years at the plant and stratified those diagnosed before or after 1995. But these and other additional analysis did not support a finding of association between prostate cancer and atrazine exposure. In conclusion, this research did not support a finding that atrazine is a likely cause of prostate cancer nor did it add any substantial evidence that would strengthen that possibility.

cc: atrazine file (080803)
Eric Olson, SRRD (H7508C)



Use of Agricultural Pesticides and Prostate Cancer Risk in the Agricultural Health Study Cohort

Michael C. R. Alavanja¹, Claudine Samanic¹, Mustafa Dosemeci¹, Jay Lubin¹, Robert Tarone¹, Charles F. Lynch², Charles Knott³, Kent Thomas⁴, Jane A. Hoppin⁵, Joseph Barker⁶, Joseph Coble¹, Dale P. Sandler⁵, and Aaron Blair¹

¹ Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD.

² Department of Epidemiology, University of Iowa, Iowa City, IA.

³ Battelle/Centers for Public Health Research and Evaluation, Durham, NC.

⁴ US Environmental Protection Agency, Research Triangle Park, NC.

⁵ National Institute for Environmental Health Sciences, Research Triangle Park, NC.

⁶ IMS, Inc., Silver Spring, MD.

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The authors examined the relation between 45 common agricultural pesticides and prostate cancer incidence in a prospective cohort study of 55,332 male pesticide applicators from Iowa and North Carolina with no prior history of prostate cancer. Data were collected by means of self-administered questionnaires completed at enrollment (1993–1997). Cancer incidence was determined through population-based cancer registries from enrollment through December 31, 1999. A prostate cancer standardized incidence ratio was computed for the cohort. Odds ratios were computed for individual pesticides and for pesticide use patterns identified by means of factor analysis. A prostate cancer standardized incidence ratio of 1.14 (95% confidence interval: 1.05, 1.24) was observed for the Agricultural Health Study cohort. Use of chlorinated pesticides among applicators over 50 years of age and methyl bromide use were significantly associated with prostate cancer risk. Several other pesticides showed a significantly increased risk of prostate cancer among study subjects with a family history of prostate cancer but not among those with no family history. Important family history-pesticide interactions were observed.

agrochemicals; fungicides, industrial; herbicides; insecticides; pesticides; prostatic neoplasms; risk

Abbreviations: CI, confidence interval; DDT, dichlorodiphenyltrichloroethane; EPTC, S-ethyl dipropylthiocarbamate; OR, odds ratio; SIR, standardized incidence ratio; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid.

Prostate cancer is the most common malignancy among men in the United States and in most Western countries (other than nonmelanoma skin cancer), and in the United States, it is the second leading cause of cancer death (1, 2). Despite the common occurrence of this tumor, its etiology remains largely unknown.

Age, family history, African-American ethnicity, hormonal factors, and possibly a high consumption of animal fat and red meat are the most consistent risk factors reported (3–10). An inverse association with vegetable and fruit consumption has been suggested (9, 11, 12), while

smoking may be related to the occurrence of fatal prostate cancer (13).

Farming has been the most consistent occupational risk factor for prostate cancer (14, 15). Farm-related potential risk factors include exposures to insecticides, fertilizers, herbicides, and other chemicals (16–23). However, the role of specific agricultural chemicals has not been firmly established because of the lack of precise exposure data (20, 21). We examined the exposure-response relation between 45 important agricultural pesticides and prostate cancer incidence in the Agricultural Health Study cohort

Reprint requests to Dr. Michael C. R. Alavanja, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS, Room 8000, Rockville, MD 20892 (e-mail: alavanjm@mail.nih.gov).

while controlling for known and suspected risk factors for prostate cancer.

MATERIALS AND METHODS

Cohort enrollment

The Agricultural Health Study is a prospective cohort study of 89,658 people, including 52,395 private applicators and 4,916 commercial applicators licensed to apply restricted use pesticides and 32,347 spouses of farmer applicators from Iowa and North Carolina (24). Private applicators were farmers or nursery workers, and "commercial" applicators were persons employed by pest control companies or businesses that use pesticides (e.g., warehouse operators, grain mills). Pesticide applicators were enrolled when they completed an enrollment questionnaire. In Iowa, both commercial and farmer applicators attend the same pesticide certification testing sessions, and both were invited to participate in the study. In North Carolina, because private and commercial applicators attend separate training, only private applicators were enrolled. Private and commercial applicators were also asked to complete "take-home" questionnaires that sought more extensive information on occupational activities. Recruitment of applicators and their spouses began in December 1993 and continued until December 1997. Male spouses are too few for meaningful analysis at this time.

Questionnaires

The enrollment questionnaire sought information on the use of 50 pesticides (ever/never), crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, smoking, alcohol consumption, fruit and vegetable intake, multiple vitamin use, medical conditions, medical conditions in first-degree relatives including a history of prostate cancer, and basic demographic data (all questionnaires are at <http://www.aghealth.org>). For 22 of the 50 pesticides in the enrollment questionnaire, we also obtained information on the duration of use (years) and frequency of use (days per year). Information on application methods and protective equipment was used to compute an exposure "intensity index I" (25). For the remaining 28 pesticides listed in the enrollment questionnaire, exposure information was limited to ever versus never used. The enrollment questionnaire also included two activities (painting and engine repair) that frequently result in exposure to solvents. The take-home questionnaires included the following: detailed use information on the 28 pesticides reported as ever/never use in the enrollment questionnaire, more detailed information on personal protective equipment use, dietary and cooking practices, supplemental vitamin use, height and weight (used for body mass index), occupational exposures to welding and solvents, nonfarm jobs, and hours spent in strenuous physical activity.

Cohort follow-up

Cohort members were matched to cancer registry files in Iowa and North Carolina for case identification and to the state death registries and to the National Death Index to ascertain vital status; prostate cancer cases diagnosed prior to enrollment were excluded from the analyses. Incident cases were identified from enrollment (i.e., 1993–1997) through December 31, 1999. Study subjects alive but no longer residing in Iowa or North Carolina were identified through personal contacts with the study subject, motor vehicle records, pesticide registration records, and the Internal Revenue Service address database (which has current address information on all Americans filing a tax return). This includes over 98 percent of the Agricultural Health Study cohort. Fewer than 0.4 percent of the cohort were lost to mortality or cancer incidence follow-up ($n = 319$).

Analysis

A standardized incidence ratio for prostate cancer was computed to compare prostate cancer incidence among male cohort members with incidence in the male populations of Iowa and North Carolina. Expected numbers for the standardized incidence ratio were developed from 5-year age and calendar-time (i.e., 1994–1998), race-specific cancer incidence rates from the population-based cancer registries in Iowa and North Carolina. The statistical significance of the standardized incidence ratios and 95 percent confidence intervals was based on standard methods (26, 27).

Because the follow-up period for case ascertainment was less than 5 years (i.e., an average of 4.3 years) and the prostate cancer incidence rate did not vary appreciably, multivariate logistic regression (28) was used to compare prostate cancer cases with noncases on a number of factors possibly associated with prostate cancer risk. In this analysis, we examined 50 pesticides, crops grown and livestock raised, personal protective equipment used, pesticide application methods used, other agricultural activities and exposures, nonfarm occupational exposures, regular recreational physical activity, smoking, alcohol consumption, red meat consumption, fruit and vegetable intakes, multiple vitamin use, medical conditions, medical conditions in first-degree relatives including a history of prostate cancer, "high pesticide exposure events" (29), age, race, state of residence, license type, education, and basic demographic data. All analyses excluded both female applicators and 414 prevalent prostate cancer cases.

Factor analysis was used to examine the interrelations among ever/never use of 50 pesticides, state (Iowa, North Carolina), and age (≤ 50 and > 50 years) (30). Only variables that shared at least 15 percent of the variance with the factor, corresponding to a factor-loading score of 0.40 or higher, were considered when interpreting the factors. Factor scores were computed for each subject and then divided into tertiles based on the factor scores for cases. The upper tertile was divided in half, and the upper half was then divided in half again to examine more extreme exposure scores (resulting in categories at ≤ 33.3 percent, 33.4–66.7 percent, 66.8–83.3 percent, 83.4–91.6 percent, > 91.6 percent). Logistic regres-

TABLE 1. Characteristics of licensed pesticide applicators in the Agricultural Health Study, 1993–1997

Characteristics*	Prostate cancer		Cohort member		Adjusted odds ratio†	95% confidence interval	p value
	Cases	%	Noncases	%			
Total (all)	566		54,766				
Age (years)							
<55	67	11.8	38,860	70.9	1.0‡		<0.0001§
55–59	78	13.8	5,374	9.8	5.2	3.1, 8.7	
60–64	139	24.6	4,581	8.4	12.8	8.1, 20.2	
65–69	159	28.1	3,165	5.8	22.4	14.2, 35.3	
70–74	77	13.6	1,804	3.3	19.6	11.4, 33.6	
≥75	46	8.1	980	1.8	25.6	13.5, 48.6	
Race							
White	546	96.5	53,425	97.6	1‡		0.50
Black and other races	20	3.5	1,341	2.4	1.55	0.5, 4.4	
Residence							
Iowa	326	57.6	35,560	64.9	1‡		0.29
North Carolina	240	42.4	19,206	35.1	0.82	0.6, 1.1	
Education (years)							
<12	97	18.6	4,669	9.1	1‡		0.36§
12	279	53.4	24,631	48.1	1.41	0.9, 2.2	
>12	147	28.1	21,958	42.8	1.35	0.8, 2.2	
License type							
Private	541	95.6	50,090	91.5	1‡		0.41
Commercial	25	4.4	4,676	8.5	1.10	0.6, 2.0	
Smoker							
Never	195	39.8	25,159	51.1	1‡		0.06§
Former	243	49.6	15,423	31.4	1.30	0.9, 1.7	
Current	52	10.6	8,629	17.5	1.42	0.9, 2.2	
Family history of prostate cancer							
No	391	81.1	45,342	91.4	1‡		0.0001
Yes	91	18.9	4,271	8.6	1.90	1.4, 2.7	

Table continues

sion analysis was performed to evaluate the association between factor scores and the risk of prostate cancer, controlling for the same potentially confounding variables as above.

Unconditional logistic regression analysis was also used to evaluate risks associated with a reported history of mixing or applying specific pesticides. We used the “never used the specific pesticide” category as the reference group and the five percentile categories described above as the exposed groups. Exposure variables for the 22 pesticides included in the enrollment questionnaire, evaluated on the entire Agricultural Health Study male cohort, included the following: 1) application days per year; 2) total years of exposure; 3) an exposure “intensity index I,” which includes information about the application method, a score for whether the applicator repaired his own pesticide application equipment, and a score for the use of protective equipment (25); and 4) a

cumulative pesticide exposure score: (application days per year) × (total years of exposure) × (exposure intensity index I). We omitted pesticides from this analysis if a total of five or fewer applicators were exposed to the chemical.

For the subset of male applicators ($n = 24,034$) who also completed the take-home questionnaires, exposure variables (for 28 additional pesticides) included the following: 1) application days per year; 2) total years of exposure; 3) an exposure “intensity index II,” which included information about mixing methods, an application methods score, whether an enclosed tractor was used in applying pesticides, whether the applicator repaired his own pesticide application equipment, whether the applicator washed his pesticide equipment, a score for the use of protective equipment, personal hygiene information, whether the applicator changed clothes after a chemical spill, and the frequency of replacing gloves (25); and 4) a cumulative pesticide expo-

TABLE 1. Continued

Characteristics	Prostate cancer		Cohort member		Adjusted odds ratio†	95% confidence interval	p value
	Cases	%	Noncases	%			
Vegetable							
<5 times/week	156	32.0	17,001	34.0	1‡		0.76§
5–7 times/week	169	34.6	18,250	36.5	0.75	0.5, 1.0	
>1/day	163	33.4	14,808	29.5	0.93	0.7, 1.3	
Red meat							
0–<2 times/week	115	35.2	7,150	30.2	1‡		0.70§
2 times/week	84	25.7	6,612	27.9	0.96	0.7, 1.4	
≥3/week	128	39.1	9,942	41.9	0.94	0.7, 1.3	
Supplemental vitamin use							
No	218	69.0	15,771	67.6	1‡		0.40§
Not regularly	38	12.0	3,556	15.2	0.92	0.6, 1.4	
Regularly	60	19.0	4,004	17.2	0.87	0.6, 1.2	
Hours of exercise/week (leisure time)							
None	120	37.5	5,678	24.2	1‡		0.23§
<1	53	16.6	4,148	17.7	0.68	0.5, 1.0	
1–1.5	46	14.4	3,978	17.0	0.80	0.5, 1.2	
1.6–4	46	14.4	4,557	19.4	0.64	0.4, 1.0	
4.1–8	32	10.0	2,792	11.9	0.86	0.5, 1.4	
>8	23	7.2	2,312	9.9	0.57	0.3, 1.0	
Body mass index							
Quartile 1 (lowest)	69	23.8	5,838	25.2	1.0‡		0.44§
Quartile 2	83	26.2	5,742	24.8	1.34	0.9, 2.0	
Quartile 3	86	27.1	5,798	25.1	1.23	0.8, 1.8	
Quartile 4 (highest)	79	24.9	5,761	24.9	1.31	0.9, 2.0	
High pesticide exposure event							
No	276	87.6	19,825	85.0	1‡		0.48
Yes	39	12.4	3,510	15.0	1.11	0.8, 1.6	

* Information on age, race, state of residence, education, license type, smoking history, family history of prostate cancer, and vegetable intake was taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 new prostate cancer cohort members; 414 cohort members had prostate cancer before enrollment into the study and were not included in this analysis. Information on high pesticide exposure events, supplemental vitamin use, hours of leisure exercise per week, body mass index, and red meat intake was taken from the farmer applicator and commercial applicator questionnaire completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members. Data reflect cohort characteristics as of December 31, 1999. Missing data for some questions are responsible for differences in total cell counts.

† Odds ratios of prostate cancer adjusted for age, race, state of residence, education, license type, smoking history, family history of prostate cancer, vegetable intake, supplemental vitamin use, body mass index, high pesticide exposure events, exercise per week, and red meat intake.

‡ Reference group.

§ p value for trend test.

sure score: (application days per year) × (total years of exposure) × (exposure intensity index II). For both algorithms, exposure-response was assessed by a linear trend test, treating the cumulative score as a continuous variable, and also by selecting the median cumulative score of each exposure category and treating the cumulative score as a categor-

ical variable. Analyses of prostate cancer risk were conducted by state and by license type in Iowa (i.e., private vs. commercial) to evaluate the consistency of findings within the cohort. All odds ratios were adjusted for age as a categorical variable (<55, 55–59, 60–64, 65–69, 70–74, and ≥75 years). Institutional review boards approved the study

TABLE 2. Risk from occupational exposures to licensed pesticide applicators off the farm and from painting and welding on the farm, Agricultural Health Study, 1993–1997

Exposure	Prostate cancer		Cohort member		Adjusted odds ratio*	95% confidence interval*	p value*
	Cases	%	Noncases	%			
<i>Off-the-farm jobs†</i>							
Pesticides‡							
No	278	95.2	20,103	90.8	1		0.27
Yes	14	4.8	2,028	9.2	0.74	0.4, 1.3	
Solvents‡							
No	267	91.4	18,138	82.0	1		0.02
Yes	25	8.6	3,993	18.0	0.60	0.4, 0.9	
Gasoline‡							
No	268	91.8	18,128	81.9	1		0.003
Yes	24	8.2	4,003	18.1	0.53	0.3, 0.8	
Asbestos‡							
No	278	95.2	20,833	94.1	1		0.50
Yes	14	4.8	1,298	5.9	0.8	0.5, 1.4	
Grain dust‡							
No	276	94.5	19,768	89.3	1		0.36
Yes	16	5.5	2,363	10.7	0.79	0.5, 1.3	
Wood dust‡							
No	275	94.2	19,725	89.1	1		0.12
Yes	17	5.8	2,406	10.9	0.68	0.4, 1.1	
Silica/sand dust‡							
No	281	96.2	21,090	95.3	1		0.76
Yes	11	3.8	1,041	4.7	1.10	0.6, 2.0	
Engine exhaust‡							
No	257	88.0	17,048	77.0	1		0.58
Yes	35	12.0	5,083	23.0	0.88	0.6, 1.4	

Table continues

proposal and the manner in which informed consent was obtained from study participants.

RESULTS

This analysis was restricted to the 55,332 male private and commercial applicators with no history of prostate cancer at enrollment. A total of 1,197 deaths occurred among male applicators during the mean follow-up period of 4.3 years. A total of 566 incident prostate cancers were observed between enrollment and December 31, 1999. Based on age-adjusted state incidence rates, 494.5 prostate cancer cases were expected, yielding a standardized incidence ratio of 1.14 (95 percent confidence interval (CI): 1.05, 1.24). For the same period, cancer incidence from all sites was significantly less than expected, with an overall standardized incidence ratio of 0.80 (95 percent CI: 0.76, 0.83). The prostate cancer standardized incidence ratio (SIR) appeared higher among commercial applicators (SIR = 1.41, 95 percent CI: 0.89, 2.11) than among private applicators (SIR = 1.13, 95 percent CI: 1.04, 1.24) and higher among Iowa Whites (SIR = 1.27,

95 percent CI: 1.13, 1.27) than among North Carolina Whites (SIR = 1.10, 95 percent CI: 0.99, 1.21). There were too few prostate cancer cases among non-Whites in North Carolina ($n = 19$) and Iowa ($n = 0$) for meaningful calculation of standardized incidence ratios at this time. For the subset of the male applicator cohort ($n = 24,034$) who completed the take-home questionnaire, the prostate cancer standardized incidence ratio of 1.22 (95 percent CI: 1.09, 1.36) and the overall cancer standardized incidence ratio of 0.81 (95 percent CI: 0.75, 0.87) were similar to those for the entire cohort.

Odds ratios for prostate cancer increased sharply with age, and cases were more likely to have a family history of prostate cancer (table 1). Nineteen percent of prostate cancer cases reported a family history of prostate cancer among first-degree relatives, compared with 8.6 percent of noncases. No other characteristic in table 1 was statistically significant after adjustment for the other characteristics shown. A nearly significant positive association was observed for cigarette smoking.

TABLE 2. Continued

Exposure	Prostate cancer		Cohort member		Adjusted odds ratio	95% confidence interval	p value
	Cases	%	Noncases	%			
Lead solder†‡							
No	281	96.2	21,172	95.7	1		0.57
Yes	11	3.8	959	4.3	0.84	0.5, 1.5	
Welding fumes‡							
No	260	89.0	18,147	82.0	1		0.25
Yes	32	11.0	3,984	18.0	0.80	0.6, 1.2	
Other metals‡							
No	281	96.2	21,340	96.4	1		0.34
Yes	11	3.8	791	3.6	1.36	0.7, 2.5	
Pneumatic drill‡							
No	284	97.3	20,550	92.9	1		0.10
Yes	8	2.7	1,581	7.1	0.55	0.3, 1.1	
No exposure off the farm reported‡							
No	232	79.5	18,541	83.8	1		0.10
Yes	60	20.5	3,590	16.2	1.27	0.9, 1.7	
			<i>On farm</i>				
Painting on farm§							
No	254	44.8	19,485	35.6	1		0.22
Yes	312	55.2	35,281	64.4	1.13	0.9, 1.4	
Welding on farm§							
No	1	51.4	19,209	35.1	1		0.33
Yes	275	48.6	35,559	64.9	0.91	0.8, 1.1	

* Odds ratios, 95% confidence intervals, and *p* values adjusted for age and family history of prostate cancer; the "no" exposure was always used as the reference category.

† Eight occupational exposures occurring off the farm including x-rays, cotton dust, mineral dust, electroplating fumes, lead, mercury, cadmium, and mixing herbicides in the military were omitted from the table because fewer than five exposed cases were observed.

‡ Information on all off-the-farm jobs/activities completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members.

§ Information on age and on family history of prostate cancer, painting (on-farm activity), and welding (on-farm activity) taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 prostate cancer cohort members; 414 cohort members had prostate cancer before enrollment into the study and were not included in this analysis. Missing data for some questions are responsible for the differences in total cell counts.

Table 2 lists odds ratios for prostate cancer by selected occupational exposures on and off the farm. No characteristic in table 2 was significantly associated with prostate cancer after adjustment for age and family history of prostate cancer.

Table 3 lists the 50 herbicides, insecticides, fungicides, and fumigants for which information concerning the frequency, duration, intensity, and cumulative exposure score was available in this study.

Results of the factor analysis showed a tendency for the use of certain pesticides to group together (table 4). Three factors explained almost 90 percent of the variance in pesticide usage in the observed data (appendix table 1). Factor 1 showed significant loading scores (i.e., correlations) with the herbicides atrazine, dicamba, cyanazine, metolachlor,

S-ethyl dipropylthiocarbamate (EPTC), alachlor, imazethapyr, 2,4-dichlorophenoxyacetic acid (2,4-D), trifluralin, chlorimuron ethyl, metribuzin, petroleum oil, pendimethalin, and butylate and with the insecticide terbufos. These are pesticides used primarily on corn, soybeans, and other grain crops, which are especially important in Iowa. Factor 2 showed significant loading scores for North Carolina residence (i.e., -70 for Iowa). Pesticides descriptive of this factor include one herbicide (paraquat), three insecticides (parathion, carbaryl, aldicarb), one fumigant (methyl bromide), and four fungicides (benomyl, chlorothalonil, maneb/mancozeb, and metylaxyl). These pesticides are used on cotton, tobacco, vegetables, and fruit crops raised mostly in North Carolina that require intensive treatment for insects, nematodes, and fungi. Factor 3 loaded heavily on study

TABLE 3. Pesticides evaluated in this study for an association with prostate cancer by frequency of use,* duration of use,† intensity of use,‡ and cumulative use,§ Agricultural Health Study, 1993–1997

Herbicides	Insecticides	Fungicides	Fumigants
Alachlor	Aldicarb	Benomyl	Aluminum phosphide
Atrazine	Aldrin	Captan	Ethylene dibromide
Butylate	Carbofuran	Chlorothanil	Carbon tetrachloride/carbon disulfide
Chlorimuron-ethyl	Carbaryl	Maneb/macozeb	Methyl bromide
Cyanazine	Chlordane	Metalaxyl	
Dicamba	Chlorpyrifos	Ziram	
2,4-D¶	Coumaphos		
EPTC¶	Dichlorvos¶		
Glyphosate	Diazinon		
Imazethypyr	Dieldrin		
Metolachlor	DDT¶		
Metribuzin	Fonofos		
Paraquat	Heptachlor		
Pendimethalin	Lindane		
Petroleum oil as herbicide	Malathion		
2,4,5-T¶	Parathion		
2,4,5-TP¶	Permethrin (for crops)		
Trifluralin	Permethrin (for animals)		
	Phorate		
	Terbufos		
	Toxaphine		
	Trichlorofon		

* Frequency as application days/year.

† Duration as years of application.

‡ Intensity as the algorithm score.

§ Cumulative exposure as the product of frequency × duration × intensity.

¶ 2,4-D, 2,4-dichlorophenoxyacetic acid; EPTC, S-ethyl dipropylthiocarbamate; dichlorvos, 2,2-dichloroethenyl dimethylphosphate; DDT, dichlorodiphenyltrichloroethane; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid.

subjects over 50 years of age; on chlorinated insecticides no longer registered for use in the United States, including aldrin, chlordane, dieldrin, dichlorodiphenyltrichloroethane (DDT), heptachlor, and toxaphene; and on two chlorinated phenoxy herbicides, 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) and 2,4,5-trichlorophenoxypropionic acid (2,4,5-TP).

Table 4 shows odds ratios for categories of factor scores and tests of linear trends adjusted for age and family history of prostate cancer. Factor 3 was significantly associated with an excess risk of prostate cancer, while factor 1 and factor 2 were not.

Table 5 displays odds ratios for the 10 pesticides for which ever versus never use data and cumulative exposure scores were available from the enrollment questionnaires. For 35 additional pesticides for which similar cumulative exposure data were available (listed in table 3), no exposure-response association with prostate cancer was observed, and they were omitted from table 5 to save space (five pesticides were excluded from the analysis because five or fewer cases were exposed (i.e., trichlorofon, ziram,

aluminum phosphide, ethylene dibromide, and carbon tetrachloride/carbon disulfide)). No meaningful differences were found in the exposure-response when analyzed as either a continuous or a categorical variable, so only the categorical analysis results are presented. We computed odds ratios adjusted for age and family history (reduced model) and for all the variables listed in table 1 (full model). Because the full model did not substantially change the odds ratio estimates for any pesticide, we provide the results from the reduced model in table 5. Among the pesticides listed in the enrollment questionnaire, only methyl bromide, a fumigant used by approximately 12 percent of the cohort, showed a significant linear trend ($p = 0.008$) with prostate cancer risk. This trend is almost entirely due to the elevated risk in the two highest exposure categories. Odds ratios were 1 (reference, no exposure), 1.01 (95 percent CI: 0.66, 1.56), 0.76 (95 percent CI: 0.47, 1.25), 0.70 (95 percent CI: 0.38, 1.28), 2.73 (95 percent CI: 1.18, 6.33), and 3.47 (95 percent CI: 1.37, 8.76). The trend in prostate cancer risk with methyl bromide did not differ by tumor grade; that is,

TABLE 4. Odds ratios, confidence intervals, and number of prostate cancer cases for factor scores, based on factor analysis of 50 pesticides, family history of prostate cancer, and age,* Agricultural Health Study, 1993–1997

Factor	Level†					<i>p</i> value, linear trend
	I (lowest exposure)	II	III	IV	V (highest exposure)	
Factor 1 (herbicides)						
Odds ratio	1.0	0.99	1.18	1.10	1.25	0.53
95% confidence interval		0.78, 1.26	0.89, 1.56	0.78, 1.55	0.88, 1.76	
No. of cases	188	189	94	48	47	
Factor 2 (fumigants/fungicides, North Carolina)						
Odds ratio	1.0	1.04	0.97	0.94	0.84	0.82
95% confidence interval		0.83, 1.30	0.74, 1.28	0.66, 1.34	0.59, 1.18	
No. of cases	188	189	95	46	48	
Factor 3 (older age, chlorinated pesticides)						
Odds ratio	1.0	1.29	1.51	1.37	1.39	0.005
95% confidence interval		1.02, 1.63	1.15, 2.00	0.96, 1.97	0.99, 1.97	
No. of cases	188	189	95	47	47	

* Adjusted for age and family history of prostate cancer.

† Levels = tertiles, with the upper tertile divided in half, and the resulting half divided in half again (levels IV and V) (i.e., level I, 0–33.3; level II, 33.4–66.6; level III, 66.7–83.3; level IV, 83.4–91.6; and level V, 91.7–100.0).

both well-differentiated tumors and poorly differentiated tumors were observed to have a significant linear trend with methyl bromide exposure ($p = 0.03$ and $p = 0.04$, respectively) (data not shown). Methyl bromide was also associated with a significantly increased risk of prostate cancer among private applicators in both states, with a linear trend p of 0.05 in North Carolina (odds ratios (ORs) for previously defined categories = 1 (reference), 0.9, 0.8, 0.7, 2.8, and 3.8) and a linear trend p of 0.04 in Iowa (ORs for previously defined exposure categories = 1 (reference), 1.7, 1.2, and 4.4; no cases in higher exposure categories), and among commercial applicators in Iowa, with a linear trend p of 0.01 (ORs for previously defined exposure categories = 1 (reference), 1.1, 3.1, 8.9, and 14.0; no cases in the highest exposure category). Similarly, significantly elevated exposure-response trends were observed for frequency of use, with $p = 0.02$ (ORs = 1 (reference), 0.93, 0.76, 1.31, 1.44, and 4.39), and lifetime application days, with $p = 0.02$ (ORs = 0.87, 0.78, 0.97, 2.09, and 2.63). The odds ratio for ever versus never use of methyl bromide data was elevated but not significantly (OR = 1.10, 95 percent CI: 0.85, 1.36).

Few differences were found between the cohort members who completed the take-home questionnaire (i.e., 40 percent applicators) and those that did not (31). These take-home questionnaires sought more detailed information on 28 pesticides (including 18 currently used pesticides and 10 pesticides no longer currently registered for use in the United States). Applicators who ever used any one of five insecticides, including three chlorinated insecticides associated with factor 3 (i.e., aldrin, DDT, and heptachlor), were at a significantly elevated risk of prostate cancer: carbofuran (OR = 1.25, 95 percent CI: 1.03, 1.52),

permethrin for animal use (OR = 1.38, 95 percent CI: 1.01, 1.89), aldrin (OR = 1.32, 95 percent CI: 1.09, 1.60), DDT (OR = 1.37, 95 percent CI: 1.12, 1.67), and heptachlor (OR = 1.20, 95 percent CI: 1.00, 1.47). Little evidence was found, however, to support an exposure-response trend for prostate cancer with the use of any pesticide other than methyl bromide (table 5), and this significant association was unchanged when other pesticides were added to the logistic model (data not shown).

To assess the possible influence of a family history of prostate cancer on pesticide-associated risks (table 6), we assessed effect modification by including a cross-product term in the logistic model, that is, age + family history + pesticide exposure + (family history \times pesticide exposure). Significant interaction odds ratios occurred among persons who used butylate (OR = 1.93, 95 percent CI: 1.19, 3.11), a widely used thiocarbamate herbicide; four commonly used organophosphorothioate insecticides including coumaphos (OR = 2.58, 95 percent CI: 1.29, 5.18), fonofos (OR = 2.04, 95 percent CI: 1.21, 3.44), chlorpyrifos (OR = 1.65, 95 percent CI: 1.02, 2.66), and phorate (OR = 1.64, 95 percent CI: 1.02, 2.63); and a pyrethroid, permethrin (for animal use) (OR = 2.31, 95 percent CI: 1.17, 4.56). Similar results were found in North Carolina and Iowa (results not shown). These associations did not change when other pesticides were added to the logistic model. Several other pesticides had nonsignificant but elevated interaction odds ratios ($p < 0.10$), including EPTC (OR = 1.68, 95 percent CI: 0.96, 2.94) (thiocarbamate herbicide), terbufos (OR = 1.52, 95 percent CI: 0.94, 2.45) (organophosphorothioate), dicamba (OR = 1.51, 95 percent CI: 0.95, 2.43) (benzoic herbicide), 2,2-dichloroethenyl dimethylphosphate (dichlorvos) (OR = 1.92, 95 percent CI: 0.98, 3.75) (organophosphate), aldcarb (OR = 2.01, 95 percent CI:

TABLE 5. Odds ratios,* confidence intervals, and number of exposed cases of prostate cancer by ever/never exposed and cumulative exposure score for methyl bromide and selected pesticides with no observed exposure-response association with prostate cancer,† Agricultural Health Study, 1993–1997

Pesticide	Ever/never use‡	Cumulative exposure score categories§ from enrollment questionnaire¶ and the farmer applicator and commercial applicator questionnaire#						<i>p</i> value, linear trend
		0 (no exposure, reference category)	I (lowest exposure)	II	III	IV	V (highest exposure)	
<i>Herbicides</i>								
Alachlor¶								
Odds ratio	1.00	1	0.91	1.11	1.35	0.70	0.77	0.52
95% confidence interval	0.83, 1.20		0.70, 1.18	0.85, 1.45	0.95, 1.92	0.44, 1.12	0.48, 1.26	
No. of cases	263/303	303	81	82	40	20	20	
Atrazine¶								
Odds ratio	0.94	1	1.02	0.91	0.89	0.82	0.97	0.34
95% confidence interval	0.78, 1.14		0.79, 1.31	0.71, 1.18	0.65, 1.23	0.54, 1.25	0.63, 1.48	
No. of cases	364/202	202	113	114	57	27	28	
<i>Insecticides</i>								
Carbofuran¶								
Odds ratio	1.25	1	1.29	1.93	1.00	0.68	1.01	0.23
95% confidence interval	1.03, 1.52		0.95, 1.74	1.42, 2.62	0.66, 1.51	0.38, 1.23	0.58, 1.77	
No. of cases	166/400	400	54	50	26	12	13	
Chlorpyrifos¶								
Odds ratio	0.90	1	0.95	1.04	0.89	0.64	0.73	0.23
95% confidence interval	0.74, 1.09		0.70, 1.30	0.75, 1.42	0.58, 1.36	0.35, 1.18	0.41, 1.31	
No. of cases	174/392	392	49	48	24	12	12	
Permethrin¶ (animal, animal confinement area application)								
Odds ratio	1.38	1	1.30	2.31	1.11	1.73	0.74	0.63
95% confidence interval	1.01, 1.89		0.76, 2.24	1.38, 3.87	0.54, 2.25	0.63, 4.75	0.24, 2.33	
No. of cases	48/518	518	16	16	8	4	4	
Aldrin#								
Odds ratio	1.32	1	1.44	1.12	1.56	0.87	1.38	0.70
95% confidence interval	1.09, 1.60		0.98, 2.11	0.76, 1.66	0.92, 2.64	0.38, 1.99	0.60, 3.19	
No. of cases	207/359	226	33	34	17	7	8	
DDT#,**								
Odds ratio	1.37	1	1.18	1.17	0.76	1.38	1.14	0.89
95% confidence interval	1.12, 1.67		0.84, 1.66	0.81, 1.69	0.46, 1.27	0.71, 2.68	0.59, 2.21	
No. of cases	323/243	178	50	45	23	11	11	

Table continues

0.95, 4.23) (carbamate insecticide), and carbofuran (OR = 1.58, 95 percent CI: 0.98, 2.55) (carbamate insecticide). No fungicide or fumigant, no chlorinated or inorganic insecticides, and no herbicides of the following chemical classes—acetamides, triazines, pyrimidines, phosphinic acids, imidazolines, bipyridyls, chlorinated phenoxyes, dinitroanilines, or aliphatic hydrocarbons—had elevated ($p < 0.10$) interaction odds ratios.

To examine the specificity of these pesticide associations with family history, we examined the risk of prostate

cancer from exposure to the same 45 pesticides, stratified by those with and without a family history of any cancer other than prostate cancer in a first-degree relative (data not shown). Only butylate (OR = 1.52, 95 percent CI: 1.13, 2.02) had a significantly elevated risk of prostate cancer in the group with a family history of cancer (other than prostate cancer), and only butylate showed significant effect modification, although a number of other nonsignificant interactions were observed. Permethrin for animal use (OR = 1.59, 95 percent CI: 1.07, 2.36) and phorate (OR = 1.31,

TABLE 5. Continued

Pesticide	Ever/never use	Cumulative exposure score categories from enrollment questionnaire and the farmer applicator and commercial applicator questionnaire						<i>p</i> value, linear trend
		0 (no exposure, reference category)	I (lowest exposure)	II	III	IV	V (highest exposure)	
Heptachlor#								
Odds ratio	1.20	1	1.08	0.86	1.00	0.64	0.66	0.41
95% confidence interval	0.99, 1.47		0.67, 1.74	0.53, 1.41	0.51, 1.98	0.20, 2.03	0.21, 2.09	
No. of cases	165/401	273	20	19	10	6	3	
<i>Fumigants</i>								
Methyl bromide¶								
Odds ratio	1.10	1	1.01	0.76	0.70	2.73	3.47	0.004
95% confidence interval	0.77, 1.36		0.66, 1.56	0.47, 1.25	0.38, 1.28	1.18, 6.33	1.37, 8.76	
No. of cases	84/482	482	23	22	11	6	5	
<i>Fungicides</i>								
Captan¶¶								
Odds ratio	1.05	1	1.07	1.09	1.89	0.95	2.79	0.11
95% confidence interval	0.78, 1.43		0.50, 2.30	0.48, 2.48	0.58, 6.12	0.23, 3.93	0.35, 22.1	
No. of cases	48/518	518	7	6	3	2	1	

* Odds ratios adjusted for age and family history of prostate cancer.

† Five pesticides (i.e., trichlorofon, ziram, aluminum phosphide, ethylene dibromide, carbon tetrachloride/carbon disulfide) were not included in this table because we observed five or fewer exposed cases. Thirty-five other pesticides (i.e., cyanazine, dicamba, 2,4-dichlorophenoxyacetic acid, thiocarbamate, glyphosate, imazethapyr, metachlor, trifluralin, coumaphos, 2,2-dichloroethenyl dimethylphosphate, fonofos, permethrin for crop use, turbufos, chlorothalonil, butylate, chlorimuron-ethyl, metribuzin, paraquat, pendimethalin, petroleum oil used as herbicide, 2,4,5-trichlorophenoxyacetic acid, 2,4,5-trichlorophenoxypropionic acid, aldicarb, carbaryl, chlordane, diazinon, dieldrin, lindane, malathion, parathion, phorate, toxaphene, benomyl, maneb/macozeb, methylaxyl) were not included in this table because they did not demonstrate a significant exposure-response association with prostate cancer.

‡ Study subjects in the ever/never analysis equal or exceed the number in the exposure-response analysis because of occasional missing data for the exposure algorithm.

§ Categories: 0 (no use), I (0.1–33.3 percentile of use), II (33.4–66.7 percentile of use), III (66.8–83.3 percentile of use), IV (83.4–91.6 percentile of use), and V (>91.6 percentile of use).

¶ Information on age, family history of prostate, ever/never use of 50 pesticides, and cumulative use of 22 pesticides taken from the enrollment questionnaire completed by 54,766 non-prostate cancer cohort members and 566 prostate cancer cohort members.

Information on cumulative pesticide use of 28 pesticides from farmer applicator and commercial applicator questionnaire completed by 24,034 non-prostate cancer cohort members and 331 prostate cancer cohort members.

** DDT, dichlorodiphenyltrichloroethane.

95 percent CI: 1.03, 1.67) were the only chemicals observed to have a significant excess risk among those with no family history of cancer, but no significant effect modification was observed (data not shown). We also examined the risk of any cancer other than prostate cancer ($n = 816$ other cancers) among those exposed to each of the 45 pesticides, stratified by a family history of any cancer (other than prostate cancer), and found little evidence of effect modification (data not shown).

DISCUSSION

The literature suggests that prostate cancer may be elevated among farmers (14, 16, 18–22, 32, 33). Consistent with these earlier reports, we found that farmers in the Agricultural Health Study cohort experienced a small but statistically significant excess of prostate cancer compared with the

general population in Iowa and North Carolina (SIR = 1.14). It is challenging to relate cancer risks to specific lifestyle or agricultural exposures. We used four approaches in this paper. First, we evaluated a broad range of factors including demographic characteristics, lifestyle factors, agricultural factors, and nonfarm occupational factors to identify associations with prostate cancer. Second, factor analysis was used to identify groupings of pesticide exposures that might be related to prostate cancer. Third, analyses of individual pesticides were conducted. Finally, effect modification was assessed between individual pesticide use and a family history of prostate cancer.

In the factor analysis, three temporally and geographically distinct factors of pesticide use were identified. Only one of these factors (factor 3) was significantly related to prostate cancer. This factor included ever use of the chlorinated pesticides aldrin, chlordane, dieldrin, DDT, heptachlor, and

TABLE 6. Odds ratios, confidence intervals, and number of prostate cancer cases by exposure status to 15 of 45* evaluated pesticides with and without a first-degree family history of prostate cancer, Agricultural Health Study, 1993–1997

Pesticide (chemical class)	Prostate cancer risk for those with exposure to pesticide but no family history of prostate cancer†			Prostate cancer risk for those with exposure to pesticide and a family history of prostate cancer‡			Statistical interaction between family history of prostate cancer and exposure to pesticide§		
	Odds ratio	95% confidence interval	No. of prostate cancer cases	Odds ratio	95% confidence interval	No. of prostate cancer cases	Interaction odds ratio	95% confidence interval	p value
<i>Herbicides</i>									
Alachlor (acetamide)	0.93	0.76, 1.14	190	1.36	0.88, 2.10	56	1.50	0.93, 2.41	0.10
Atrazine (triazine)	0.88	0.72, 1.09	253	1.28	0.77, 2.12	70	1.52	0.88, 2.62	0.13
Butylate (thiocarbamate)	0.96	0.77, 1.20	110	1.78	1.16, 2.73	44	1.93	1.19, 3.11	0.007
Dicamba (benzoic)	0.95	0.77, 1.17	163	1.35	0.88, 2.08	50	1.51	0.95, 2.43	0.09
EPTC¶	0.90	0.67, 1.20	55	1.44	0.89, 2.34	24	1.68	0.96, 2.94	0.07
<i>Insecticides</i>									
Aldicarb (carbamate)	0.81	0.57, 1.16	35	1.60	0.83, 3.09	11	2.01	0.95, 4.23	0.07
Carbofuran (carbamate)	1.14	0.92, 1.42	118	1.81	1.18, 2.77	43	1.58	0.98, 2.55	0.06
Chlorpyrifos (organophosphorothioate)	0.82	0.66, 1.02	121	1.29	0.84, 1.98	40	1.65	1.02, 2.66	0.04
Coumaphos (organophosphorothioate)	0.86	0.57, 1.28	26	2.17	1.24, 3.82	16	2.58	1.29, 5.18	0.008
2,2-Dichloroethyl dimethylphosphate (organophosphate)	0.95	0.66, 1.37	32	1.75	1.00, 3.06	16	1.92	0.98, 3.75	0.06
Fonofos (organophosphonodithioate)	0.92	0.71, 1.19	71	1.80	1.14, 2.84	30	2.04	1.21, 3.44	0.008
Permethrin, animal use (pyrethroid)	1.13	0.77, 1.66	30	2.38	1.34, 4.25	16	2.31	1.17, 4.56	0.02
Phorate (organophosphorodithioate)	1.05	0.85, 1.30	140	1.67	1.09, 2.56	48	1.64	1.02, 2.63	0.04
Terbufos (organophosphorodithioate)	0.99	0.80, 1.23	126	1.45	0.95, 2.23	40	1.52	0.94, 2.45	0.09
<i>Fumigants</i>									
Methyl bromide (halogenated hydrocarbon)	0.93	0.70, 1.23	58	1.31	0.75, 2.29	16	1.36	0.73, 2.54	0.34

* Five pesticides (i.e., trichlorofon, ziram, aluminum phosphide, ethylene dibromide, carbon tetrachloride/carbon disulfide) were not included in this table because we observed five or fewer exposed cases. Thirty other pesticides (i.e., chlorimuron-ethyl, cyanazine, 2,4-dichlorophenoxyacetic acid, glyphosate, imazethapyr, metachlor, trifluralin, permethrin for crop use, chlorothalonil, metribuzin, paraquat, pendimethalin, petroleum oil used as herbicide, 2,4,5-trichlorophenoxyacetic acid, 2,4,5-trichlorophenoxypropionic acid, aldrin, carbaryl, chlordane, diazinon, dieldrin, dichlorodiphenyltrichloroethane, heptachlor, lindane, malathion, parathion, toxaphene, benomyl, captan, maneb/macozeb, methylalxyl) were not included in this table because they did not demonstrate a significant exposure-response association with prostate cancer.

† Reference group, no family history of prostate cancer and no pesticide exposure.

‡ Reference group, family history of prostate cancer and no pesticide exposure.

§ Adjusted for age and family history of prostate cancer.

¶ EPTC, S-ethyl dipropylthiocarbamate.

toxaphene; ever use of two chlorinated phenoxy herbicides (2,4,5-T and 2,4,5-TP); and farmers over the age of 50 years. Three of the chlorinated insecticides in this factor, that is, aldrin, DDT, and heptachlor, were associated with a significant excess risk of prostate cancer in ever/never analyses, although no exposure-response pattern was observed for these chemicals. Because the factors in this analysis are based on ever versus never use (pesticide) data, they would be more apt to show statistical significance if several chemicals in the factor had the same association with prostate cancer. Lacking an exposure-response pattern with indi-

vidual pesticides suggests that the relation with chlorinated pesticides could be due to other exposures not identified in this analysis.

Among the 45 specific pesticides evaluated, the only statistically significant exposure-response trend observed occurred with methyl bromide. This could be a chance observation because we evaluated a large number of pesticides. However, methyl bromide was significantly associated with prostate cancer risk among both North Carolina and Iowa pesticide applicators and among both private and commercial applicators. The association was also found

when we used other measures of exposure, including frequency of use (days per year) and total days of use in a lifetime. Moreover, the pattern of risk was not substantially changed when other pesticides were added to the logistic model with methyl bromide. Methyl bromide is an alkylating agent (34), and the National Institute for Occupational Safety and Health considers it to be a potential occupational carcinogen (35). Additionally, evidence of genotoxicity was observed in a small cross-sectional study of nonsmoking methyl bromide fumigation workers, with excesses of micronuclei and gene mutations (i.e., *HPRT* mutations) observed in the lymphocytes and oropharyngeal cells of exposed workers (36). Field testing by the National Institute for Occupational Safety and Health demonstrates that concentrations of methyl bromide in the breathing zones of agricultural workers conducting soil fumigation under tarpaulins (a common soil fumigation procedure used by many farmers in North Carolina but not in Iowa) frequently exceeded the recommended occupational limits set by the Institute (37). Approximately 27,000 tons of methyl bromide were used in 1997 in the United States for soil fumigation (87 percent), commodity and quarantine treatment (8 percent), and structural fumigation (5 percent) (38). Our data would suggest that, if methyl bromide is responsible for an elevated prostate cancer risk, it may be among only those with relatively frequent use. Because we had no specific a priori hypothesis linking methyl bromide to prostate cancer, we cannot rule out the possibility that our observation occurred by chance alone; however, the consistency of the findings argues against this.

A family history of prostate cancer among first-degree relatives conferred a twofold excess risk of prostate cancer on these subjects, consistent with other reports (8). Furthermore, significant associations between specific pesticides and prostate cancer risk were observed largely among those with a family history of prostate cancer. Although a family history of cancer other than prostate cancer seemed to have a similar pattern of prostate cancer risk with some pesticides, only butylate had a statistically significant positive association. No pattern of effect modification was seen when we evaluated all cancers, other than prostate, and a history of cancer other than prostate cancer. These findings tend to mitigate the possibility of a family history-driven case-recall bias in these data. The specificity for family history of prostate cancer suggests the possibilities of familial genes that enhance susceptibility or of shared environmental risk factors for prostate cancer among family members. The significant effect modification in selected chemical classes (e.g., thiocarbamates, organophosphorothioates, and pyrethroid) lends further support to this hypothesis.

This study does have limitations. First, the exposure weightings used in our algorithm are based on a literature review and not on direct measurements of exposure made within the study cohort. An exposure-monitoring effort within the study cohort is under way and will help to refine our estimates of exposure in the future. Second, some subjects in this study were asked to recall pesticide use from years ago. For the oldest members of the cohort, this was decades earlier. Although recall can be faulty after

many years, previous evaluation of this issue has shown that recall of pesticide use by the Agricultural Health Study cohort is comparable with the recall of other variables, such as diet and alcohol consumption, which have been used by epidemiologists in other studies as a standard procedure (39). Third, follow-up of this cohort is relatively short, and it is not possible to evaluate time-dependent exposures and risk.

The Agricultural Health Study has five principal strengths. First, the data collection prior to the diagnosis of cancer precludes the possibility of case-ascertainment bias. Second, detailed information on exposure for each pesticide included days of use per year, years of use, application methods, and protective equipment use, adding specificity to the analysis. Third, ascertainment of and statistical adjustment for other occupational, demographic, and lifestyle factors previously suggested as prostate cancer risk factors mitigate the possibility of uncontrolled confounding. Fourth, the large size of the study gives sufficient statistical power to examine the risk of exposure to a number of specific chemical exposures. Fifth, the outcome is cancer incidence obtained from population-based tumor registries, which eliminates survival problems.

In conclusion, farmers and commercial pesticide applicators have a small but significantly higher rate of prostate cancer than the general population of Iowa and North Carolina. Occupational use of a widely used halogenated fumigant, methyl bromide, was shown to be significantly associated with a risk of prostate cancer in the Agricultural Health Study cohort among those with the highest exposure. A pattern of chlorinated pesticide use may also be related to prostate cancer risk. A family history of prostate cancer appeared to significantly modify the prostate cancer risks among those using several widely used insecticides, including chlorpyrifos, coumaphos, fonofos, phorate, and permethrin for animal use, and a herbicide, butylate. The methyl bromide and family history findings are novel and unexpected and need to be confirmed in later follow-up periods in this cohort and in other studies of prostate cancer in farmers.

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(Appendix follows)

APPENDIX

APPENDIX TABLE 1. Results of factor analysis for pesticide use, age, and state ($n = 42,948$), Agricultural Health Study, 1993–1997*

Variable	Factor I	Factor II	Factor III
Herbicides			
Atrazine	58†	0	1
Dicamba	54†	-23	3
Cyanazine	55†	-12	4
Metolachlor	59†	8	-11
EPTC‡	48†	-8	-2
Alachlor	49†	10	3
Imazethapyr	60†	-22	-11
Glyphosate	31	27	-5
Trifluralin	60†	-2	-2
2,4-D‡	47†	0	8
Chlorimuron ethyl	54†	17	-13
Metribuzin	65†	-1	3
Paraquat	19	51†	4
Petroleum oil	44†	12	12
Pendimethalin	50†	30	-15
Butylate	52†	9	8
2,4,5-TP‡	6	10	44†
2,4,5-T‡	6	0	56†
Insecticides			
Permethrin (crop)	32	30	-8
Terbufos	40†	-1	4
Fonofos	30	-9	12
Trichlorfon	2	10	2
Carbofuran	30	16	16
Chlorpyrifos	31	22	0
Coumaphos	9	1	16
Permethrin (animal)		23	-58†
Dichlorvos‡	18	-5	21
Lindane	14	6	36
Malathion	34	16	16
Parathion	6	40†	25
Carbaryl	11	44†	17
Diazinon	7	39	25
Aldicarb	5	61†	-5
Phorate	36	-2	19
Aldrin	9	-7	65†
Chlordane	0	18	53†
Dieldrin	-1	0	59†
DDT‡	-11	11	62†
Heptachlor	10	-13	65†
Toxaphene	6	27	43†

Table continues

APPENDIX TABLE 1. Continued

Variable	Factor I	Factor II	Factor III
Fumigants			
Methyl bromide	-11	59†	-3
Aluminum phosphide	14	16	15
80/20 mix	2	11	38
Ethylene dibromide	-2	31	25
Fungicides			
Chlorothalonil	2	53†	-11
Captan	14	16	9
Ziram	-5	23	22
Benomyl	-3	61†	6
Mancozeb	-8	58†	10
Metlaxyl	-1	62†	-3
State of Iowa	36	-70†	10
Age of ≥50 years	-21	-11	52†
% of variance explained	0.44	0.30	0.15
% of cumulative variance	0.44	0.74	0.89

* Factor loadings are multiplied by 100 and rounded to the nearest integer.

† Indicates a factor loading score of greater than or equal to ± 0.40 .

‡ EPTC, S-ethyl dipropylthiocarbamate; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-TP, 2,4,5-trichlorophenoxypropionic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; dichlorvos, 2,2-dichloroethyl dimethylphosphate; DDT, dichlorodiphenyltrichloroethane.

A Nested Case–Control Study of Prostate Cancer and Atrazine Exposure

Patrick A. Hessel, PhD

Renee Kalmes, CIH

Thomas J. Smith, PhD

Edmund Lau, MS

Pamela J. Mink, PhD, MPH

Jack Mandel, PhD, MPH

Elevated prostate cancer incidence was found at a plant producing atrazine that had an intensive prostate screening program. This study tested the relationship among atrazine exposure, prostate cancer, and the screening program. Twelve cases and 130 control subjects were selected from the original cohort. Prostate screening and occupational histories were abstracted from company records and atrazine exposures were estimated. Hire date was comparable for cases and control subjects. Nearly half of the control subjects and no cases left before the prostate-specific antigen (PSA) screening program. Cases had more PSA tests than control subjects (odds ratio for ≥ 1 test, 8.54; 95% confidence interval, 1.69–82.20). There was no association between atrazine exposure and prostate cancer when those with ≥ 1 test were compared. There was no evidence for an association between atrazine and prostate cancer. (J Occup Environ Med. 2004;46:379–385)

Atrazine, one of the triazine herbicides, is the most commonly used herbicide in the United States, with 74 to 80 million pounds applied in 1999.¹ The International Agency for Research on Cancer evaluated the carcinogenicity of atrazine in humans in 1999 and concluded that it was not classifiable (ie, group 3).² However, a recent study of cancer incidence at a plant producing atrazine in Louisiana raised questions regarding a possible link with prostate cancer.³

An earlier cohort mortality study of the Louisiana plant and another plant in Alabama found no deaths from prostate cancer in a follow up of approximately 5000 workers from 1960 through 1982.⁴ An extended mortality follow up through 1993 did not report prostate cancer mortality.⁵ However, in a subsequent report by the same investigators,³ it was noted that the previous study⁵ found 3 prostate cancer deaths, with 3.1 expected. Mortality follow up at the Louisiana plant (2213 workers) was extended through 1997.⁶ There was 1 observed prostate cancer death compared with 0.5 expected.

The study of cancer incidence at the Louisiana plant (2045 workers) observed 11 prostate cancers, with 6.3 expected on the basis of local rates (standardized incidence ratio, 1.75; 95% confidence interval [CI] = 0.87–3.12).³ The excess was found in the group of workers employed directly by the plant (“company workers”) and was not found in 2 groups of contract workers. The investigators suggested that the increase in prostate cancer incidence

From Exponent, Wood Dale, Illinois (Dr Hessel, Ms Kalmes, Mr Lau, Drs Mink and Mandel); and Environmental Science and Engineering Program, Harvard School of Public Health, Boston, Massachusetts (Dr Smith).

Address correspondence to: Patrick A. Hessel, PhD, Exponent, 185 Hansen Court, Wood Dale, IL 60191; E-mail Address: phessel@exponent.com.

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might be the result of a comprehensive medical surveillance program at the plant that included the prostate-specific antigen (PSA) test because: 1) the prostate cancer cases were concentrated in the company workers who were eligible for the surveillance program; 2) most cancers were asymptomatic at the time of diagnosis; 3) most cancers were localized; 4) the cases were relatively young compared with the usual age distribution of prostate cancer cases; 5) cases were concentrated in the time period covered by the screening program; 6) all 8 of the original 11 cases who were diagnosed after 1993 (the year that PSA testing began in earnest) had undergone PSA testing; and 7) there is no biologic mechanism linking atrazine exposure to prostate cancer.

Little data exist on the relationship between atrazine and prostate cancer in agricultural workers. A study of 55,332 male pesticide applicators from Iowa and North Carolina found no association between prostate cancer incidence and self-reported atrazine exposure (odds ratio [OR], 0.94; 95% CI = 0.78–1.14 for ever vs. never use).⁷ A nested case-control study of prostate cancer among predominantly Hispanic members of a farm workers union in California did not report results for atrazine, but reported a significantly elevated odds ratio for another triazine herbicide: simazine (OR, 1.53; 95% CI = 1.02–2.28).⁸ Exposure was inferred from data on work locations of the study subjects and records of pesticide use by county. An ecologic study in California found a significant correlation between the amount of atrazine applied annually per county and cancer incidence for black males.⁹ However, the correlation coefficients were below zero for white, Hispanic, and Asian men.

The present report describes a case-control study nested within the cohort at the Louisiana facility that produced atrazine.³ The objective was to explore the relationship be-

tween atrazine exposure and prostate cancer while accounting for the potential confounding effects of the screening program.

Methods

Selection of Study Subjects

The cancer incidence study defined 3 groups of workers ($n = 2045$).³ Company workers ($n = 757$) were generally full-time, year-round workers and were eligible for the company's medical screening program (including prostate screening). The work patterns of the 2 groups of contract workers ($n = 1288$) were less regular, and they were not eligible for the company's medical screening program. The increase in prostate cancer incidence was only among the company workers. The present study was, therefore, limited to the company workers.

The previous study found 11 prostate cancer cases through 1997, with 8 of these among company workers.³ Six additional cases were observed among company workers in 1998 and 1999, bringing the total among company workers to 14. Of the 14, 12 were known to the company medical department and consented to release of their records. The remaining 2 were not known to the company. The present study, therefore, included the 12 company workers whose prostate cancers were known to the company.

Control subjects ($n = 130$) were selected randomly from the company workers and individually matched to the cases by race and year of birth (as closely as possible within 5 years). Control subjects had to begin work at the plant before the date of diagnosis of their respective cases. Cases were eligible for selection as control subjects for cases whose date of diagnosis was before their own. The number of control subjects per case ranged from 3 to 14. One case with an early year of birth had only 3 eligible control subjects. For the remainder of the cases, 10 to 14 control subjects were selected.

Company Data

For each PSA test and digital rectal examination (DRE) in the company files, the date of the test and the result were abstracted for each study subject.

Work histories were abstracted (blinded to case-control status) to the date of diagnosis for cases and to the same date for their matched control subjects. Abstracts of the work histories were independently verified. From the work histories, 341 unique combinations of job title and department were generated. This list did not identify the individuals, and did not indicate whether the titles related to cases or control subjects.

Exposure Assessment

Each of the 341 unique combinations of job title and department was placed into 1 of 5 categories of relative exposure opportunity by an industrial hygienist and 3 long-term workers at the plant. These 4 people worked independently and were blinded to the case-control status of work history entries. Raters were asked to place the job/department combinations into exposure categories without regard to potential changes in exposure over time. The 5 exposure opportunity categories were: 1) no exposure to atrazine during normal work activities; 2) occasional exposure, but normal activities did not involve exposure; 3) regular exposure to lower levels; 4) regular exposure to intermediate levels; and 5) regular exposure to higher levels.

Three of the 4 raters agreed on the exposure category for 255 (75%) of the 341 job/department combinations. The 4 raters met to discuss the remaining 86, resulting in consensus on an additional 48 (14%). Thirteen (4%) of the remaining combinations were resolved when information was provided on the time period for the job/department. The remaining 24 (7%) were classified by examining the job/department entry in the context of the individuals' full work

histories blinded to case–control status.

Seventeen workers were listed as packaging technicians without indication of whether they worked in powder or liquid packaging. Their names and time periods of interest were forwarded to 2 long-term workers at the plant who consulted, as necessary, with others to determine where these individuals had worked. For 14, the type of packaging could be identified with confidence. For the remaining 3, exposure time was split equally between liquid and powder packaging.

The higher exposures (category 5) were found in powder packaging. Most of the workers in that area were contract workers. Intermediate exposures (category 4) were generally in the atrazine production area. Workers with lower exposures (category 3) included those who worked in areas where atrazine was produced or packaged but did not have direct contact with atrazine. Workers in exposure category 2 generally worked in offices but visited the production or packaging areas infrequently. Those in category 1 did not come into the production or packaging areas.

Although the basic production process has changed little from the time the plant opened in 1970, a number of changes have occurred to limit worker exposures. These included automation for packaging of powder products, process changes designed to minimize production upsets, ventilation enhancements, the introduction of shower/change rooms, and implementation of policies related to personal protective equipment.

Industrial hygiene sampling was focused primarily on the powder packaging and atrazine production areas. Both personal and fixed location samples of total airborne dust were collected from the early 1970s. A sampling method specific to atrazine was introduced in the early 1990s and total dust sampling was phased out. There were few concur-

rent samples of atrazine and total dust. There were 1368 total dust measurements from 1970 to 1991 and 194 measurements of airborne atrazine from 1989 to 1999.

An experimental program to monitor a urinary metabolite of triazines was implemented from 1991 to 1998. These data supplemented the industrial hygiene data and covered some jobs that were not part of the air-monitoring program.

Personal measurements of total dust were used as the best indication of changes in atrazine exposure over time because they were collected consistently over time. During most of the period when total dust measurements were collected, the products contained 80% to 90% atrazine and there were no other major sources of dust.

Because the exposure data had an approximate lognormal distribution, differences across jobs and years were described using the geometric mean (GM) and geometric standard deviation (GSD). Figure 1 illustrates the mean and 95% confidence intervals for total and atrazine dust concentrations for 1975 through 1999. Examination of total dust and atrazine measurements indicated a downward trend, showing a clear reduction by 1984 with low levels thereafter.

Based on review of the major process and work activity changes, data on total dust and atrazine dust levels, urine monitoring, and policies related to personal protective equipment, a job-exposure matrix was developed. Numeric scores ranged from 10 for higher exposures in the earlier time period to 0.005 for no exposure (Table 1).

For each worker, 3 exposure metrics were calculated: time-weighted average intensity of exposure (using the scores in Table 1), duration of exposure (in days), and cumulative exposure, defined as the product of intensity and duration, summed over all jobs. Exposures were calculated up to the date of diagnosis of the case and to the same date for their respec-

tive, matched control subjects (Table 2). Additionally, exposures were calculated to 6 months before the date of diagnosis of the case to account for tumor latency.

Data Analysis

To clarify the role of prostate screening and employment patterns on prostate cancer, a series of crosstabulations was produced, comparing cases and control subjects for the intensity of screening, and dates of hire and termination. Atrazine exposure variables were compared for cases and control subjects using conditional logistic regression, controlling for age at the date of diagnosis of the case, to account for a small residual case–control difference. Exposure variables were entered as continuous variables. General linear models were used to compare mean values of the exposure variables within the matched groups. The group variable was used as a blocking variable, and case–control status (the dependent variable) was assessed for statistical significance.

To further account for the potential screening bias, the analyses of the exposure variables were repeated after eliminating those who had not had a PSA test (2 cases, 82 control subjects).

Results

Cases and control subjects were comparable for year of hire (Table 3). However, there was a marked difference in the year of termination (Table 4). None of the cases and approximately half of the control subjects terminated employment before 1990.

The numbers of DREs and PSA tests per subject were higher among cases than control subjects (Table 5). The means (standard deviations) for the number of DREs were 14.9 (4.2) for cases and 9.0 (7.0) for control subjects; and for PSA tests, the values were 3.6 (2.8) for cases and 1.6 (2.4) for control subjects (both $P < 0.05$). All but 1 of the 12 cases had 10 or more DREs.

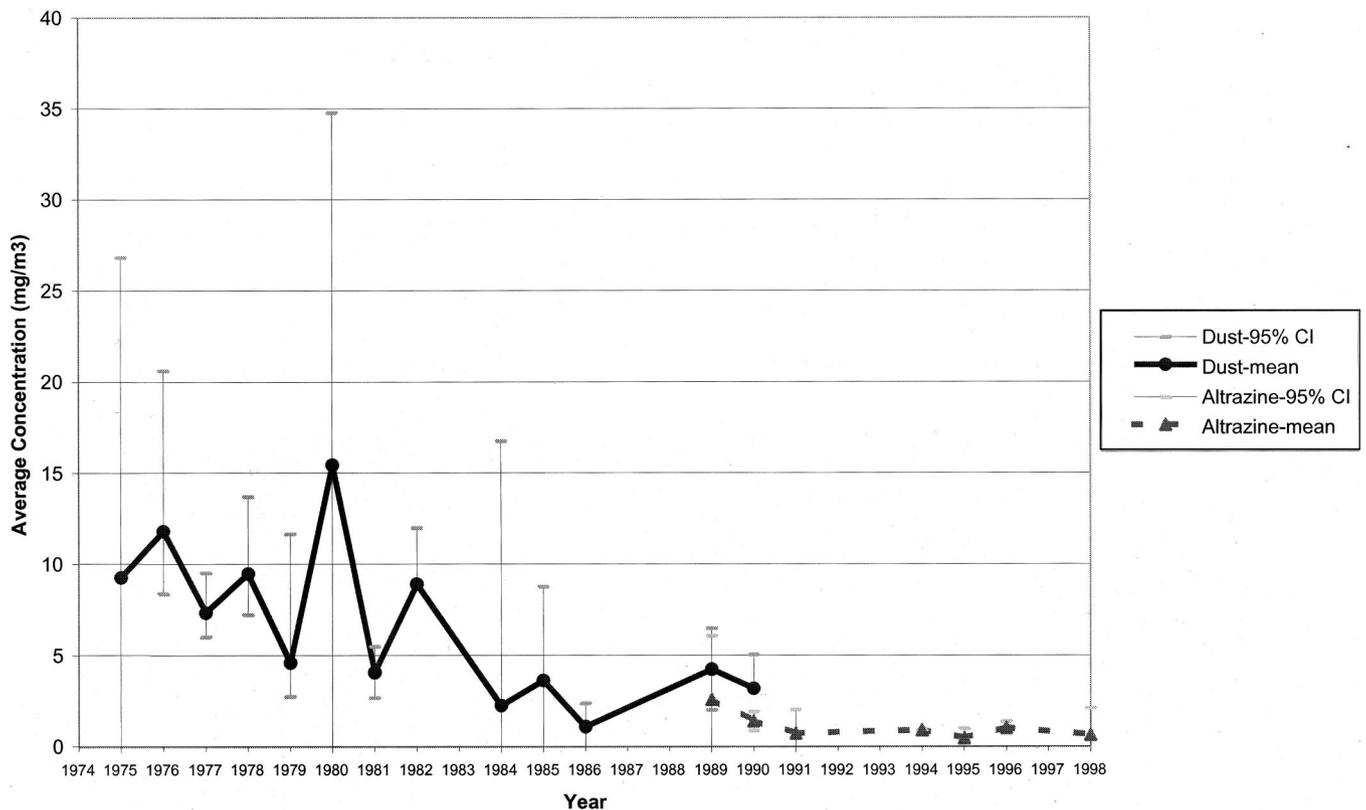


Fig. 1. Levels of total dust and airborne atrazine in the powder packaging area.

TABLE 1

Matrix of Relative Exposure

Exposure categories	1970–1984	1985–1999
(5) Regular exposure to higher levels	10	1.25
(4) Regular exposure to intermediate levels	1.6	0.8
(3) Regular exposure to lower levels	0.5	0.25
(2) Occasional exposure, but normal activities do not involve exposure	0.05	0.02
(1) No exposure during normal work activities	0.005	0.005

Only 2 of the 12 cases (16.7%) did not have a PSA test compared with 82 of the 130 control subjects (63.1%). The odds ratio for a diagnosis of prostate cancer associated with ever/never having had a PSA test was 8.54 (exact 95% CI = 1.69–82.20). Even among those who terminated in the 1990s or were still working at the end of the follow-up period, cases were more likely to have had a PSA test (OR, 2.23; exact 95% CI = 0.42–22.54). The odds ratio of 8.54 is relevant for clarifying the results of the previous cancer incidence study because it quantified the impact of the screening program

at the plant on the entire cohort. Furthermore, it provided useful information for interpreting the results of comparisons of exposure between cases and control subjects. Specifically, it indicated that the most meaningful exposure comparisons would be obtained by contrasting cases and control subjects who had participated in the program.

When all cases and control subjects were included in the analyses, there was no difference in average exposure, but length of exposure was significantly higher among cases whether using conditional logistic regression (Table 6) or general linear

models (Table 7). Cumulative exposure did not differ significantly between cases and control subjects with either analytical approach. When the analyses were limited to those with at least 1 PSA test, none of the exposure measures differed significantly between cases and control subjects for either analytical strategy.

Discussion

MacLennan et al.³ reported an increased incidence of prostate cancer in workers at the Syngenta plant producing atrazine in St. Gabriel, Louisiana. Several factors were

TABLE 2
Means, Standard Deviations (SDs), and Percentile Values for Exposure Metrics for Cases and Controls

Exposure metric*	n	Mean	SD	Percentile		
				25	50	75
All subjects (group)						
Average						
Cases	12	0.661	1.029	0.018	0.274	0.979
Controls	130	0.862	1.633	0.007	0.085	1.600
Duration						
Cases	12	7.116	2.262	5.295	7.085	8.744
Controls	130	4.488	3.249	1.286	4.086	6.880
Cumulative						
Cases	12	5.755	10.308	0.114	2.506	6.759
Controls	130	3.861	8.307	0.033	0.389	2.645
Subjects with ≥1 PSA** test						
Average						
Cases	10	0.535	1.090	0.005	0.205	0.328
Controls	48	0.791	1.326	0.008	0.158	0.879
Duration						
Cases	10	7.232	2.478	4.389	7.747	8.976
Controls	48	7.156	2.485	5.116	6.952	9.372
Cumulative						
Cases	10	5.219	11.309	0.022	1.701	3.078
Controls	48	6.635	11.652	0.035	0.873	6.380

* Average exposure analyzed using relative exposure units as defined in Methods section. Duration of exposure = days from start of exposure to date of diagnosis of the case, divided by 1,000. Cumulative exposure = days at job × exposure intensity, summed over all jobs, divided by 1,000.

** PSA = prostate-specific antigen.

TABLE 3
Distribution of Year of Hire for Cases and Controls

Year	Cases		Controls	
	n	%	n	%
1970–74	5	41.7	67	51.5
1975–79	4	33.3	39	30.0
1980–84	0	—	11	8.5
1985+	3	25.0	13	10.0
Total	12	100	130	100

listed indicating that the excess was probably the result of the intensive screening program that included PSA testing. However, the investigators acknowledged their inability to definitively exclude a role for atrazine given that measures of exposure had not been determined for individuals in the cohort. The present study addressed the confounding effect of the screening program while estimating atrazine exposures and assessing exposures in relation to prostate cancer. The results demonstrated that the prostate screening program

TABLE 4
Distribution of Year of Termination for Cases and Controls

Year	Cases		Controls	
	n	%	n	%
1970–74	0	—	18	13.8
1975–79	0	—	18	13.8
1980–84	0	—	21	16.2
1985–89	0	—	5	3.8
1990–94	1	8.3	8	6.2
1995+*	11	91.7	60	46.2
Total	12	100	130	100

* Includes those still employed.

confounded the results of the study of cancer incidence, and when confounding was removed, there was no evidence for a relationship between atrazine exposure and prostate cancer.

Characteristics of the Study

The number of prostate cancer cases in the present study precluded subgroup analyses; however, the results using continuous exposure vari-

ables were not suggestive of an association between atrazine and prostate cancer. The use of continuous exposure variables enhanced the ability to discern case–control differences. Sample size and statistical power would have been a more important concern if non-significant, but potentially important differences were found between cases and control subjects. No suggestive case–control differences in exposure were observed.

The industrial hygiene and urine monitoring data facilitated reconstruction of historical exposures. The measurements were largely limited to airborne dust in 2 areas with higher exposures, ie, powder packaging and atrazine production. Despite changes in measurement methods over time, the data provided a consistent pattern of relative differences between job categories, and they showed continued improvements in hygiene conditions over time. There were few measurements in the jobs with lower expo-

TABLE 5

Comparison of Cases and Controls by Number of Digital Rectal Examinations (DRE) and Prostate-Specific Antigen (PSA) Tests

Number of tests	DRE				PSA			
	Cases		Controls		Cases		Controls	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
0	0	—	12	9.2	2	16.7	82	63.1
1	0	—	9	6.9	3	25.0	7	5.4
2	0	—	12	9.2	0	—	4	3.1
3	0	—	8	6.2	0	—	6	4.6
4–6	0	—	18	13.8	5	41.7	25	19.2
7–9	1	8.3	7	5.4	2	16.7	6	4.6
10–12	4	33.3	19	14.6	0	—	0	—
13–15	2	16.7	15	11.5	0	—	0	—
16–18	2	16.7	17	13.1	0	—	0	—
19–21	2	16.7	8	6.2	0	—	0	—
22–24	1	8.3	4	3.1	0	—	0	—
25+	0	—	1	0.8	0	—	0	—
Total	12	100	130	100	12	100	130	100

TABLE 6

Odds ratios and 95% confidence intervals for time-weighted average exposure, duration of exposure, and cumulative exposure comparing cases to their matched controls*

Measure of exposure	Odds ratio	95% CI	<i>P</i> -value
All subjects (12 cases, 130 controls)			
Average exposure	0.87	0.46–1.30	0.69
Duration of exposure	1.30	1.06–1.66	0.01
Cumulative exposure	1.01	0.95–1.07	0.62
Those with ≥1 PSA test (10 cases, 48 controls)			
Average exposure	0.82	0.36–1.47	0.56
Duration of exposure	0.96	0.71–1.30	0.77
Cumulative exposure	0.98	0.91–1.05	0.68

* Odds ratios calculated using conditional logistic regression controlling for age, with exact methods for calculating confidence intervals. Each exposure variable was tested in a separate model.

Average exposure analyzed using relative exposure units as defined in Methods section.

Duration of exposure = days from start of exposure to date of diagnosis of the case, divided by 1,000.

Cumulative exposure = days at job × exposure intensity, summed over all jobs, divided by 1,000.

ures. However, the relatively low exposure levels in all jobs outside of packaging and atrazine production meant that the estimation of atrazine levels for these jobs had little impact on estimates of average and cumulative exposure scores (ie, average exposures were largely determined by the amount of time spent in the higher exposure jobs).

Effect of Prostate Screening

To explore the effect of screening, it was necessary to consider case–

control differences in employment patterns. Because the PSA screening program was introduced in the early 1990s, only those workers who were at the plant during that time period were able to participate. The data in Table 3 indicated that cases and control subjects were fairly comparable with regard to year of hire, with many being hired within the first 5 years of operation of the plant. On the other hand, there was a marked difference in year of termination between cases and control subjects (Ta-

ble 4). The control subjects exhibited a steady migration out of the plant from the outset, whereas all of the cases remained at the plant until the 1990s, thus making themselves available for repeat PSA screening.

Both DREs and PSA tests were more common among cases than control subjects (Table 5). The high odds ratio for the association between having at least 1 PSA test and case–control status suggested that the PSA screening program alone could have accounted for the standardized incidence ratio observed in the cancer incidence study.³ Considering that 2 of the prostate cancers among company workers in that study were not detected by the screening program, it could be argued that they should have been included in this analysis as not having been detected by PSA. Even if they had been included, the odds ratio for PSA screening in relation to prostate cancer would have been 4.27 (exact 95% CI = 1.14–19.49). The magnitude of the screening effect observed in this study was comparable to that observed in other settings.^{10,11}

Atrazine Exposure

After accounting for the confounding effect of PSA screening, there

TABLE 7

Comparison of Mean Values for Exposures for Cases and Their Matched Controls Using General Linear Models to Account for Matching*

Measure of exposure	Average values		Difference	P-value
	Cases	Controls		
All subjects (12 cases, 130 controls)				
Average exposure	0.66	0.86	-0.20	0.68
Duration of exposure	7.12	4.49	2.63	0.01
Cumulative exposure	5.76	3.86	1.89	0.46
Those with ≥ 1 PSA test (10 cases, 48 controls)				
Average exposure	0.54	0.79	-0.26	0.57
Duration of exposure	7.23	7.16	0.08	0.93
Cumulative exposure	5.22	6.64	-1.42	0.73

* See notes for Table 6 for definitions of exposure measures.

was no relationship between exposure to atrazine and prostate cancer. The data on case-control differences in employment patterns and the relationship between duration of employment and PSA testing demonstrated that the most appropriate analyses were those limited to cases and control subjects who had undergone PSA testing. These comparisons showed no differences in any measure of exposure between cases and control subjects, regardless of the analytical strategy.

Several supplementary analyses were conducted to further explore the relationship between atrazine and prostate cancer (data not shown). One analysis compared the amount of time spent in powder packaging for cases and control subjects, and a second focused on amount of time in powder packaging during the period before 1985, when exposures in powder packaging were highest. Neither analysis demonstrated significant or suggestive case-control differences. Another analysis limited to the 5 cases and 71 control subjects whose exposures began at least 20 years before the date of diagnosis of the cases demonstrated no case-control differences, except the ex-

pected difference in duration of exposure associated with the screening effect.

Conclusion

There is no evidence for an association between atrazine exposure and prostate cancer among the workers.

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