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Aromatic amine pesticide use and human cancer risk: results from the U.S. Agricultural Health Study

Stella Koutros[1], **Charles F. Lynch**[2], **Xiaomei Ma**[3], **Won Jin Lee**[4], **Jane A. Hoppin**[5], **Carol H. Christensen**[6,7], **Gabriella Andreotti**[1], **Laura Beane Freeman**[1], **Jennifer A. Rusiecki**[8], **Lifang Hou**[9], **Dale P. Sandler**[5], and **Michael C.R. Alavanja**[1]

[1] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services. Rockville, MD. USA.

[2] University of Iowa, College of Public Health, Iowa City, IA. USA.

[3] Division of Environmental Health, Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, CT. USA.

[4] Department of Preventive Medicine, College of Medicine, Korea University, Seoul, Korea.

[5] Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC. USA.

[6] United States Environmental Protection Agency, USA

[7] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland. USA.

[8] Uniformed Services University of the Health Sciences, Bethesda, MD, USA

[9] Department of Preventive Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL. USA.

Abstract

Imazethapyr, a heterocyclic aromatic amine, is a widely used crop herbicide first registered for use in the United States in 1989. We evaluated cancer incidence among imazethapyr-exposed pesticide applicators enrolled in the Agricultural Health Study. The Agricultural Health Study is a prospective cohort of 57,311 licensed pesticide applicators in the U.S., enrolled from 1993-1997. Among the 49,398 licensed pesticide applicators eligible for analysis, 20,646 applicators reported use of imazethapyr and 2,907 incident cancers developed through 2004. Imazethapyr exposure was classified by intensity-weighted lifetime exposure days calculated as [years of use × days per year × intensity level]. Poisson regression analysis was used to evaluate the relationship between imazethapyr exposure and cancer incidence. We found significant trends in risk with increasing lifetime exposure for bladder cancer (p for trend 0.01) and colon cancer (p for trend 0.02). Rate ratios were increased by 137% for bladder cancer and 78% for colon cancer when the highest exposed were compared with the nonexposed. The excess risk for colon cancer was limited to proximal cancers, (Rate Ratio =2.73, 95% confidence intervals 1.42, 5.25, p for trend 0.001). No association was observed for prostate, lung, rectum, kidney, oral, pancreas, lymphohematopoietic cancers or melanoma. These findings provide new evidence that exposure to aromatic amine pesticides may be

Corresponding Author Michael C.R. Alavanja Occupational and Environmental Epidemiology Branch Division of Cancer Epidemiology and Genetics, National Cancer Institute 6120 Executive Blvd., EPS 8000, MSC 7240 Rockville, MD 20852, USA. Phone: 301-435-4720 Fax: 301-402-1819 .

an overlooked exposure in the etiology of bladder and colon cancer. The use of imazethapyr and other imidazolinone compounds should continue to be evaluated for potential risk to humans.

Keywords

pesticides; bladder; colon; occupational exposures

INTRODUCTION

Occupational aromatic amine exposure has long been recognized as a causative factor for bladder cancer and several specific aromatic amine compounds have been implicated as human bladder carcinogens.[1] Since these discoveries exposure to heterocyclic aromatic amines (HCA) and the presence of toxic HCA-DNA adducts in several organ tissues, including the colon, prostate and pancreas among others, has been hypothesized to increase the risk of cancer.[2] Despite the evidence implicating several HCA's as carcinogenic, not all of these compounds are equally harmful. Thus, several HCA compounds are still used in occupation settings. Among farmers, pesticide application of the compound imazethapyr is one such example.

Imazethapyr is an herbicide used to control weeds in corn, soybean, dry bean, alfalfa, and other crops.3 Imidazolinone compounds like imazethapyr are an emerging class of herbicides known for their low acute toxicity. Since the registration of imazethapyr with the United States (U.S.) Environmental Protection Agency (EPA) in 1989, the number of acres in the U.S. treated with imazethapyr has steadily increased. It is consistently one of the most widely used herbicides among soybean and legume vegetable producers.[4] Approximately 42% of participants in the U.S. Agricultural Health Study (AHS), a prospective cohort of licensed pesticide applicators from Iowa and North Carolina, reported use of imazethapyr, making it one of the most commonly used pesticides in this cohort. This chemical is also registered for use in several countries worldwide including Canada, Australia, New Zealand, South Africa, Tanzania, India, and Indonesia among others.5

The general public can be exposed to residues of imazethapyr in food and in drinking water through groundwater contamination.[6] Of 16 sulfonylurea, sulfonamide, and imidazolinone herbicides evaluated in 75 surface water and 25 ground water sites in Iowa and Illinois, imazethapyr was the most frequently detected compound in both states.[7] This chemical has also been found to contaminate surface waters in agricultural areas in Alberta, Canada.[8] While residues in food are regulated, ground water contamination by imazethapyr is far less well characterized despite its persistence and mobility in laboratory environmental fate studies.[9]

Information about the health effects of imazethapyr is limited. The U.S. EPA currently characterizes imazethapyr as an unlikely carcinogen based on two carcinogenicity studies conducted in mice and rats over an 18-24 month period.[10] There is no evidence of mutagenicity or genotoxicity with exposure to imazethapyr in animal models.[6] In light of its widespread use, it is important to examine potential cancer risks associated with exposure to this aromatic amine pesticide particularly for bladder cancer. The Agricultural Health Study cohort offers a unique setting in which to examine this question, with frequent and well-characterized occupational exposures.

MATERIALS AND METHODS

Study Population

The AHS is a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. A detailed description of this cohort has been described elsewhere.[11] Briefly,

applicators were recruited from December 1993 through December 1997. Participants completed a self-administered enrollment questionnaire which provided detailed exposure data, including information on the use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, basic demographics and lifestyle factors, family history of cancer, and information on the use of 50 different pesticides, including imazethapyr. Cohort members were linked 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. Residence information was obtained from motor vehicle records, pesticide registration records, and address files of the Internal Revenue Service. Eighty-two percent of the target population was successfully recruited and less than 2% of the cohort has been lost to follow-up by moving out of either state. This analysis includes all incident cancers diagnosed from enrollment (1993-1997) through December 31, 2004. Follow-up was censored at the time of participant death, movement out of state, or December 31, 2004 (average follow-up time is 9.2 yrs). All participants provided informed consent, and the protocol was approved by the institutional review boards of all participating institutions.

Exposure Assessment

Exposure to imazethapyr was quantified using information from a self-administered questionnaire. This questionnaire collected comprehensive use data on 22 pesticides, including imazethapyr, and ever/never use information for 28 additional pesticides. Participants were asked how many years they applied imazethapyr (1year or less, 2-5, or 6-10 years) and how many days it was personally used in an average year (less than 5, 5-9, 10-19, 20-39, 40-59, 60-150, or more than 150 days). Additional information was collected on a wide variety of exposures, lifestyle factors and other basic demographic characteristics. The questionnaires used for this analysis were the Phase I 'Enrollment Questionnaire,' the 'Farmer Applicator Questionnaire,' and the 'Commercial Applicator Questionnaire,' which can be accessed at http://aghealth.org/questionnaires.html.

We used an intensity-exposure algorithm to quantify pesticide exposure. Intensity levels were estimated using questionnaire data from enrollment and measurement data from the published pesticide exposure literature and the Pesticide Handlers Exposure Database,12 as follows: intensity level = [(mixing status + application method + equipment repair status)×personal protective equipment use]. Mixing status was defined as never, <50% of the time mixed, or 50%+ of the time mixed (scored 0,3,9). Application method was defined as does not apply, applies via various methods subset by pesticide type: herbicide, crop insecticide, animal insecticide, fungicides, fumigants (scored 0-9). Repair status was scored 0 for does not repair and 2 for repairs. Personal protective equipment use was categorized based on information provided on the questionnaire regarding glove, goggle, face shield, boots, mask or other use of protective clothing or equipment (score 0.1-1.0). The total value that the intensity score can have ranges from >0-20. A more detailed discussion of the algorithm factors and an example is provide in Dosemeci et al.[13] Lifetime exposure days (LED) of imazethapyr use were calculated as [years of use × days per year]. LED were combined with the measure of intensity to create intensity-weighted lifetime exposure days (IWED) as follows: LED×intensity level. In order to optimize statistical power and to have sufficient numbers of cases in each analytic group, IWED was categorized into tertiles based on the exposure distribution among all exposed cancer cases. IWED categories are defined as: <54.1 (T1), 54.1 to <152.9 (T2), 152.9 to <311.9 (T3 lower half), and ≥ 311.9 (T3 upper half). To improve resolution at higher exposures, we divided the highest category at the median whenever there were at least 10 exposed cases in the highest exposure category. We also examined risk separately by days of use per year, years of use, and intensity level. The cutpoints for categorizing these metrics were also based on the distribution among exposed cases for all cancers combined.

Data Analysis

Only incident cancers were considered in this analysis (n=2,907) thereby excluding 1,084 prevalent cases of cancer at baseline. Applicators who did not provide information on imazethapyr exposure or were missing exposure algorithm information were excluded (n=6,544) as were applicators with missing information on age or person-years of follow-up (n=285), leaving 49,398 individuals available for analysis. Poisson regression analysis was used to calculate rate ratios (RR) and 95% confidence intervals (95% CI) describing the relationship between imazethapyr exposure and cancer incidence. A given cancer was evaluated if it had more than a total of 15 exposed cases for IWED categories (prostate, lung, colon, rectum, bladder, non-Hodgkin lymphoma, leukemia, melanoma, kidney, oral, pancreas, and all lymphohematopoietic cancers combined: leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma, and multiple myeloma). Rate ratios were adjusted for confounding variables if the variable changed the parameter estimates for the main exposure by more than 10%; models for individual cancer sites differed based on this criterion. Factors evaluated for possible confounding included age at enrollment (<40, 40-49, 50-59, >= 60), gender, state, enrollment year, applicator type (commercial or private, due to varying exposure profiles), education, family history of any cancer in first-degree relatives (yes/no), family history of individual/given cancer for specific analyses (yes/no), alcohol consumption during the past 12 months (ever, never, missing), cigarette smoking history (never, former smoker, current smoker, missing), race (white, other, missing), body mass index, sun exposure, aspirin intake, fruit and vegetable intake, lifetime exposure days to all pesticides (0-105, >105-368, >368) and top ten pesticides correlated with imazethapyr based on lifetime exposure days and categorized by tertile of exposure: permethrin (crops), fonofos, trichlorfon, carbofuran, glyphosate, metolachlor, EPTC, alachlor, pendimethalin, and trifluralin. Models for colon and rectal cancers were additionally adjusted for ever use of chlorpyrifos and aldicarb which have been previously found to be associated with colorectal cancer in AHS analyses.[14] Categorical cutpoints are listed for only those potential confounders that were retained in models.

We used two reference groups to address potential residual confounding due to unmeasured differences between the exposed and unexposed applicators. These groups were as follows: 1) those reporting no use or exposure to imazethapyr, which offers more statistical power and 2) those in the lowest exposure category. We also performed analyses restricted to applicators in Iowa given the predominance of imazethapyr use in this state. For lung cancer and bladder cancer we performed a finer adjustment for cigarette smoking (never, former smoker <5 pack-years, former smoker 5-30 pack-years, former smoker >30 pack-years, current smoker <15 pack-years, current smoker 15-45 pack-years, current smoker >45 pack-years, missing).

Additional anatomic subsite analyses were performed for colon cancer: right-sided or proximal colon cancer (ICD-O-2 codes C18.0-C18.4 which includes cecum, appendix, ascending colon, hepatic flexure, and transverse colon) and left-sided or distal colon cancer (ICD-O-2 codes C18.5-C18.7 which includes the splenic flexure, descending colon, and sigmoid colon). Colon cancers of unspecified origin and overlapping lesions of the colon were excluded (n=10) in anatomic subsite analyses.

Tests for trend were conducted using the midpoint value of each exposure category where it was treated as a continuous response in Poisson regression models. All p-values are two-sided and rate ratios and 95% confidence intervals were calculated using SAS statistical software (SAS Institute, Inc., Cary, North Carolina) from AHS data release version PIREL0612.

RESULTS

Selected characteristics of the study population are presented in Table 1. During 452,439 person years of follow-up, 20,646 (42%) applicators reported exposure to imazethapyr. Imazethapyr

was most often reported for use on field corn, soybean, hay and alfalfa crops (data not shown). The most common application methods for imazethapyr include, boom on tractor/trailer/truck, hand spray gun, and in furrow or banded application (data not shown). Exposed applicators reported an average of 8.8 days per year, 4.2 years of use, and 260.0 intensity-weighted lifetime exposure days of imazethapyr. The majority were white male private applicators and 94% of the exposed applicators were from Iowa. Alcohol consumption was reported more frequently by exposed applicators than by nonexposed applicators. Differences between the exposed and nonexposed groups were small with respect to age, applicator type, education level, smoking history, and family history of cancer.

Rate ratios and 95% CI's for risk of selected cancers associated with intensity-weighted lifetime exposure days of imazethapyr using the nonexposed referent groups for comparison are presented in Table 2. The incidence of all cancers combined was marginally increased with increasing imazethapyr use; the RR comparing the highest exposure group with the nonexposed was 1.13 (95% CI: 0.96-1.34), and the p for trend was 0.14. A significantly elevated risk of colon cancer was observed among those in the highest tertile of imazethapyr exposure (RR = 1.78, 95% CI: 1.08-2.93, p for trend 0.02). Risk of bladder cancer was also significantly elevated when the highest exposed group was compared with the nonexposed (RR = 2.37, 95% CI: 1.20-4.68, p for trend 0.01). Risks in the highest exposed groups for bladder cancer and colon cancer where slightly higher when restricting analyses to Iowa applicators only, RR= 2.59, 95% CI: 1.21-5.54 and RR= 1.85, 95% CI: 1.06-3.26, respectively (not shown). Nonsignificant but elevated risks were observed for all lymphohematopoietic cancers (RR = 1.23, 95% CI: 0.77-1.98) and leukemia (RR = 1.63, 95% CI: 0.72-3.69) when the highest exposed was compared with the nonexposed. Imazethapyr was not associated with the risk of prostate, melanoma, lung, rectum, non-Hodgkin lymphoma, kidney, oral, or pancreatic cancer.

We also explored using the lowest exposed group as the referent in an attempt to control for residual confounding. Findings from analyses using the lowest exposed group as the referent and those using the LED metric were similar to those using the IWED metric and are therefore not shown. Analyses examining risk separately by days of use per year, years of use, and intensity level yielded no additional information.

Rate ratios and 95% CI's for risk of colon cancer and imazethapyr intensity-weighted lifetime exposure days by subsite are presented in Table 3. We found a statistically significant increased risk of proximal colon cancer associated with imazethapyr when the highest exposed group was compared with the nonexposed, RR=2.73 (95% CI 1.42-5.25), as well as a significant dose-response relationship for increasing imazethapyr use (p for trend 0.001). There was no significant elevation in risk of distal cancer (RR = 1.21, 95% CI: 0.55-2.68; Table 3) or rectal cancer (RR=0.77, 95% CI 0.39-1.51; Table 2) comparing the highest imazethapyr exposed group to the nonexposed.

DISCUSSION

Significant excess risks of bladder and colon cancers were observed in the Agricultural Health Study among applicators exposed to the heterocyclic aromatic amine herbicide imazethapyr. For bladder cancer, participants in the highest exposure category of imazethapyr had a 137% higher risk than nonexposed pesticide applicators. For colon cancer, detailed analysis by subsite revealed that imazethapyr use was significantly associated with a 173% increased risk of proximal cancers, but not with distal or rectal cancers.

Although bladder cancer risk has been reported to be elevated in some agricultural populations, [15] this is the first report of a significant increase in bladder cancer specifically linked to the pesticide imazethapyr. While there is the possibility that this could be a chance finding, other

aromatic amines are well established in the etiology of bladder cancer. Significant excess bladder cancer risks have been observed among those employed in aromatic amine manufacture, dyestuff manufacture and use, rubber manufacture, painting, aluminum industry, leather industry and truck driving.[16,17] Many of these excess risks are related to two specific aromatic amines, benzidine and 2-naphthylamine. Among workers exposed to these compounds, the time between first exposure and death due to bladder cancer ranged from 12 to 41 years suggesting that the current duration of exposure to imazethapyr, which was first available in 1989, may be adequate for cancer development.[18]

Farmers generally have significantly lower risk of bladder cancer and colon cancer than the general population, possibly due to lower rates of smoking and increased levels of physical activity; however, studies of colon cancer and pesticides have been inconsistent.[19-24] Previous analyses in the AHS cohort have linked increased risks of colon cancer with exposure to dicamba[25] and aldicarb.[14] Evidence linking HCA exposure to colon cancer comes from the dietary literature. Meat cooked at high temperature results in increased formation of HCA compounds and increased intake of well-cooked meat has been positively associated with colon cancer risk.[26-28] Inside the body, HCAs are activated to carcinogenic intermediates via xenobiotic metabolizing enzymes. A similar mode of action may be at work for imazethapyr metabolism but no human metabolism data are available for this compound.

We also found that the excess risk of colon cancer observed was largely due to cancers occurring in the proximal colon. There are well described differences in the incidence and risk factors for proximal and distal colon cancers.[29,30] Although no studies have identified HCA pesticide exposure as a risk factor for proximal colon cancer, a body of evidence suggests that proximal cancers are associated with certain molecular events that may be related to pesticide exposure. Proximal cancers are more often associated with microsatellite instability, an accumulation of errors at microsatellite loci, whereas distal cancers tend to exhibit chromosomal instability manifested by aneuploidy and loss of heterozygosity.[29,30] Microsatellite instability results from the loss of DNA mismatch repair due to altered methylation and subsequent silencing of MHL1.[31,32] Pesticide exposure has also been linked to altered methylation in several animal studies.[33-35] Thus, it is plausible that imazethapyr exposure, through altered DNA methylation mechanisms, may be linked to excess proximal versus distal colon cancers. However, there is also the possibility that these findings are due to chance given the small number of cases observed.

The AHS has several unique strengths. The study population is large and frequently exposed to pesticides. Comprehensive histories of pesticide use in terms of duration, frequency, and intensity of exposure were collected for a variety of different pesticides prior to the onset of cancer. Information on a number of other potential confounders including other occupational and lifestyle factors (i.e. smoking) was also collected. The participation rates at recruitment (82%) and follow-up (less than 2% lost to follow up) were very high. Self-reported pesticide use information has been found to be reliable in this cohort.[36,37] However, it has been noted that 5% of users of imazethapyr have inaccurate information with respect to duration of use, or years of use. To address this issue we performed a sensitivity analysis excluding those subjects with total years that exceeded the number of years since first registration and found no difference is risk estimates. As in many occupational settings, applicators are not exposed to just one chemical agent; however, we were able to control for potential confounding from other pesticides by both adjusting for use of highly correlated pesticides and by using the lowest exposed groups as the referent for comparison. In addition, we were able to use detailed smoking history information to finely control for smoking status as this is an independent risk factor for bladder cancer in the AHS cohort.

A few limitations are worth noting. Although some exposure misclassification is inevitable, exposure information was obtained prior to onset of cancer and thus, misclassification is likely to be nondifferential with a resulting bias toward the null. While we did observe an increase in risk in the highest exposure category for leukemia, this result was not significant and has only few exposed cases, thus we are unable to make any definitive conclusions about potential risk. Similarly, we were unable to evaluate certain cancers due to small numbers of exposed cases. Continued follow-up of the cohort will aide in following up any suggestive findings for leukemia as well as evaluations for cancers that we could not assess at this time. Additionally, this analysis consists of predominantly white males potentially limiting generalizability to women and other race/ethnic groups.

Since imazethapyr first became available in the U.S. in 1989 consideration must be given to the relatively short duration of its exposure. Out of the 41 exposed bladder cancer cases, 37 were diagnosed in 1998 or later, approximately ten years from imazethapyr's registration on the market. While this is still less than the 15-20 year latency expected for the development of solid tumors, further analyses of days of use, years of use, and intensity of use modeled separately all indicated that greater frequency, duration and intensity were associated with increased risks of cancer of the bladder and the colon lending consistency to the findings. We additionally explored the latency question by exploring an analysis where cases of bladder cancer diagnosed within approximately ten years of imazethapyr registration were excluded, thus we only included cases diagnosed in 1999 or later. Results from this sensitivity analysis indicate a similar and slightly larger magnitude of effect for imazethapyr on bladder cancer risk, RR in the highest exposure group compared with never users = 3.15 95% CI: 1.48, 6.69. An alternative explanation, however, could be that imazethapyr is acting as a promoter of the malignant phenotype rather than as a true initiator. Given that we observe an increased association with days per year as well as intensity for both cancers this promoting role could be plausible. To further explore this we attempted to consider a stratified analysis by smoking status for bladder cancer as this is a major established risk factor for this cancer. Due to small numbers, we were not able to due a true stratified analysis by smoking status (never, former, current), but when we excluded current smokers from analyses, the effect for imazethapyr and increased bladder cancer persisted in direction and magnitude thus still implicating this chemical as a potential initiator of carcinogenesis. Continued follow-up of the cohort will aide in further investigation of this alternative hypothesis.

In conclusion, we found a significantly increased risk of cancers of the bladder and colon among applicators using the aromatic amine pesticide, imazethapyr. However, there is still no biologic or experimental evidence that this pesticide is carcinogenic. These findings provide new evidence for the possible role of a widely used heterocyclic aromatic amine compound in the etiology of these cancers. Since a large portion of the world's work force is estimated to be farmers, most of whom are regularly exposed to pesticides, this newly emerging class of HCA compounds deserve further examination in biologic and epidemiologic fields; the continued follow of this cohort to accrue more total cases and more exposed cases is necessary.

Novelty Statement: While several other aromatic amine compounds are well documented risk factors for bladder and colon cancer, we believe that our findings provide new evidence that exposure to an aromatic amine pesticide, imazethapyr, may be an overlooked exposure in the etiology of these cancers. We were able to use highly detailed exposure information on occupational pesticide exposure among pesticide applicators in the U.S. Agricultural Health study, which is one of the most comprehensive databases for this information worldwide.

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Abbreviations

(AHS)	Agricultural Health Study
(LED)	Lifetime exposure days
(IWED)	Intensity-Weighted Lifetime Exposure Days
(EPA)	Environmental Protection Agency
(OR)	Odds Ratio
(CI)	Confidence Interval
(RR)	Rate Ratio

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Table 1

Characteristics of imazethapyr-exposed farmers by exposure category in the Agricultural Health Study, 1993-2004[a,b]

Characteristic	Nonexposed		Exposed	
	No. (n=28,752)	%	No. (n=20,646)	%
Mean years of follow-up	9.2		9.1	
Mean days of imazethpayr use per year (range)			8.8 (3-200)	
Mean years of imazethapyr use (range)			4.2 (1-8)	
Mean intensity weighted days (range)			260.6 (0.5-78400)	
Age at enrollment				
<40	9,504	33	8,269	40
40-49	7,639	27	6,158	30
50-59	6,041	21	3,825	19
60+	5,568	19	2,394	11
Gender				
Male	27,630	96	20,476	99
Female	1,122	4	170	1
Race				
White	27,439	95	20,330	98
Black	751	3	63	<1
Other[c]	484	2	217	1
Missing	78	<1	36	<1
State of Residence				
Iowa	14,295	50	19,355	94
North Carolina	14,457	50	1,291	6
Applicator Type				
Private	26,072	91	18,852	91
Commercial	2,680	9	1,794	9
Smoking History				
Never	14,380	50	12,037	58
Former	7,960	28	5,307	26
Current	5,231	18	2,927	14
Missing	1,181	4	375	2
Alcohol Intake in past 12 months				
Never	10,946	38	4,137	20
Ever	17,265	60	16,372	79
Missing	541	2	137	1
Education				
High School/GED or less	16,261	57	10,583	51
Beyond High School	11,814	41	9,750	47
Missing	677	2	313	2

Characteristic	Nonexposed		Exposed	
	No. (n=28,752)	%	No. (n=20,646)	%
Family History of Any Cancer				
No	16,060	56	11,778	57
Yes	10,580	37	8,098	39
Missing	2,112	7	770	4

[a] Restricted to those without previous cancer diagnosis

[b] Follow-up through 2004 (range of follow-up years >0-11)

[c] Includes Hispanic, American Indian, Alaskan Native, Asian or Pacific Islander, and Other

Table 2

Rate Ratios for selected cancers by intensity-weighted lifetime exposure days (IWED) to imazethapyr among AHS participants, 1993-2004[a]

Cancer Site	IWED	Cases	Multivariate Adjusted RR (95% CI)
All Cancers [b]	No Exposure	1919	1.00
	T1	328	0.95 (0.84, 1.07)
	T2	318	1.02 (0.91, 1.16)
	T3 (lower half)	172	1.00 (0.86, 1.18)
	T3 (upper half)	170	1.13 (0.96, 1.34)
	p for trend		0.14
Prostate [c]	No Exposure	745	1.00
	T1	148	1.04 (0.87, 1.25)
	T2	136	1.04 (0.87, 1.26)
	T3 (lower half)	73	1.05 (0.82, 1.35)
	T3 (upper half)	59	1.06 (0.81, 1.40)
	p for trend		0.97
Lung [d]	No Exposure	212	1.00
	T1	30	1.24 (0.82, 1.88)
	T2	21	0.92 (0.57, 1.50)
	T3 (lower half)	11	1.05 (0.56, 1.97)
	T3 (upper half)	11	1.01 (0.54, 1.88)
	p for trend		0.92
Colon [e]	No Exposure	141	1.00
	T1	22	0.90 (0.57, 1.41)
	T2	26	1.20 (0.79, 1.85)
	T3 (lower half)	13	1.09 (0.61, 1.95)
	T3 (upper half)	18	1.78 (1.08, 2.93)
	p for trend		0.02
Rectum [f]	No Exposure	73	1.00
	T1	14	1.04 (0.58, 1.86)
	T2	12	0.97 (0.52, 1.81)
	T3 (lower half)	10	0.77 (0.39, 1.51)
	p for trend		0.81
Melanoma [g]	No Exposure	64	1.00
	T1	11	0.85 (0.45, 1.61)
	T2	16	1.36 (0.78, 2.36)
	T3 (lower half)	10	1.38 (0.71, 2.71)
	T3 (upper half)	7	1.08 (0.49, 2.37)
	p for trend		0.58
Bladder [h]	No Exposure	81	1.00

Cancer Site	IWED	Cases	Multivariate Adjusted RR (95% CI)
	T1	12	0.99 (0.53, 1.83)
	T2	10	0.94 (0.48, 1.83)
	T3 (lower half)	7	1.29 (0.58, 2.86)
	T3 (upper half)	12	2.37 (1.20, 4.68)
	p for trend		0.01
All lymphohematopoietic [i]	No Exposure	187	1.00
	T1	29	0.71 (0.47, 1.07)
	T2	30	0.78 (0.52, 1.17)
	T3 (lower half)	17	0.77 (0.46, 1.30)
	T3 (upper half)	23	1.23 (0.77, 1.98)
	p for trend		0.41
Leukemia [j]	No Exposure	63	1.00
	T1	9	0.76 (0.38, 1.54)
	T2	12	1.21 (0.65, 2.27)
	T3 (lower half)	6	1.15 (0.49, 2.71)
	T3 (upper half)	7	1.63 (0.72, 3.69)
	p for trend		0.19
NHL [k]	No Exposure	80	1.00
	T1	15	0.95 (0.55, 1.66)
	T2	13	0.91 (0.50, 1.64)
	T3 (lower half)	7	0.83 (0.34, 1.80)
	T3 (upper half)	11	1.44 (0.76, 2.74)
	p for trend		0.35
Kidney [l]	No Exposure	58	1.00
	T1	7	0.61 (0.28, 1.34)
	T2	11	1.07 (0.56, 2.06)
	T3	10	0.91 (0.46, 1.79)
	p for trend		0.39
Oral Cavity [m]	No Exposure	45	1.00
	T1	12	1.50 (0.78, 2.88)
	T2	8	1.07 (0.49, 2.30)
	T3	7	0.82 (0.36, 1.85)
	p for trend		0.70
Pancreas [n]	No Exposure	34	1.00
	T1	5	0.80 (0.31, 2.05)
	T2	6	1.07 (0.44, 2.55)
	T3	7	1.20 (0.52, 2.74)
	p for trend		0.74

Abbreviations (alphabetical): Agricultural Health Study (AHS); Confidence Interval (CI); Rate Ratio (RR). IWED categories are defined as: <54.1 (T1), 54.1 to <152.9 (T2), 152.9 to <311.9 (T3 lower half), and ≥ 311.9 (T3 upper half).

[a] Adjusted for age at and year of enrollment.

[b] Additionally adjusted for race, family history of cancer, smoking status, applicator type, alachlor, and lifetime days of pesticide exposure.

[c] Additionally adjusted for race, family history of prostate cancer, applicator type, alachlor, and carbofuran use.

[d] Additionally adjusted for state, smoking status, and education level.

[e] Additionally adjusted for race, chlorpyrifos, and aldicarb.

[f] Additionally adjusted for smoking status, alcohol intake, aldicarb, chlorpyrifos, pendimethalin, and permethrin use.

[g] Additionally adjusted for race and family history of any cancer.

[h] Additionally adjusted for race, applicator type, smoking status, and metolachlor.

[i] Includes non-Hodgkin lymphoma, Hodgkin lymphoma, leukemia, and multiple myeloma. Additionally adjusted for alcohol intake and atrazine use.

[j] Additionally adjusted for lifetime days of pesticide exposure.

[k] Additionally adjusted for race.

[l] Additionally adjusted for gender and family history of any cancer.

[m] Additionally adjusted for race, gender, alcohol intake, and smoking status.

[n] Additionally adjusted for smoking status, and family history of any cancer.

Table 3

Relative risks for colon cancer by imazethapyr intensity weighted lifetime exposure days (IWED) and site of origin among AHS participants, 1993-2004[a]

Cancer Site	IWED	Cases (n)	Multivariate Adjusted RR (95% CI)[b]
Proximal Colon[c]	No Exposure	64	1.00
	T1	13	1.27 (0.69, 2.34)
	T2	17	1.90 (1.09, 3.29)
	T3 (lower half)	7	1.45 (0.65, 3.21)
	T3 (upper half)	11	2.73 (1.42, 5.25)
	p for trend		0.001
Distal Colon[d]	No Exposure	69	1.00
	T1	8	0.61 (0.29, 1.27)
	T2	9	0.76 (0.38, 1.54)
	T3 (lower half)	5	0.75 (0.30, 1.88)
	T3 (upper half)	7	1.21 (0.55, 2.68)
	p for trend		0.75

Abbreviations (alphabetical): Agricultural Health Study (AHS); Confidence

Interval (CI); Rate Ratio (RR). IWED categories are defined as: <54.1 (T1), 54.1 to <152.9 (T2), 152.9 to <311.9 (T3 lower half), and ≥ 311.9 (T3 upper half).

[a] Excludes Not Otherwise Specified Colon (n=6) and Overlapping lesion of colon (N=4).

[b] Adjusted for age, enrollment year, and race, chlorpyrifos use and aldicarb use.

[c] Includes cecum, appendix, ascending colon, hepatic flexure and transverse colon.

[d] Includes splenic flexure, descending colon and sigmoid colon.