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Cancer incidence among paraquat-exposed pesticide applicators in the Agricultural Health Study

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Abstract

Paraquat (1,1'-dimethyl-4, 4'-bipyridinium dichloride), a nonselective herbicide, was once widely used in North America and is still used in some countries including the U.S.A. It is extremely toxic in animals and humans after acute exposure. Although there is little evidence that paraquat is a carcinogen, exposure has been associated with some types of cancer in humans, including melanoma, leukemia, and cancers of the penis, cervix and lung. We examined the relationship between cancer incidence and lifetime exposure to paraquat among 56,222 licensed pesticide applicators from Iowa and North Carolina enrolled in the Agricultural Health Study. Poisson regression was used to calculate rate ratios (RRs) and 95% confidence intervals (CIs) among paraquat users compared to non-users, while adjusting for potential confounders. There was no risk for cancer overall, nor for any of the cancers suggested by earlier epidemiologic studies. However, risk for non-Hodgkin's lymphoma (NHL) was significantly elevated (RR=1.51, [95% CI=1.01–2.26]) when we compared those who ever used paraquat to those who never used paraquat. Among the 24,665 applicators (43.9%) who provided more detailed paraquat exposure information, those in the highest tertile of lifetime exposure-days (LE) and intensity-weighted lifetime exposure-days (IWLE) for paraquat had an increased risk of NHL, but the RRs were not significant (RR=1.74 [0.69–4.42] for LE; RR=1.86 [0.68–5.11] for IWLE, respectively) and there was not a significant exposure-response trend. Although we found some evidence for a link between paraquat exposure and NHL in this study, we cannot rule out the possibility that this is a chance finding.

INTRODUCTION

Paraquat (1,1'-dimethyl-4,4'-bipyridylium chloride dichloride; CAS 1910-42-5) is a quick-acting and non-selective herbicide (Bromilow 2004). Its use has been restricted in several countries, including Indonesia (1990), South Korea and Hungary (1991), Germany (1993), the U.S.A (1997), and Chile (2001). Nevertheless, it can still be used in the U.S.A. and some

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other countries (U.S. Dept. of Agriculture/National Agricultural Statistics Service, 2005; Pesticide Action Network (PAN) International, 2005).

Paraquat is extremely toxic in both animals and humans and has resulted in a high mortality rate after acute exposure (60–80%) (Vale et al., 1987; Lin 1990). In animal studies, paraquat has caused oxidative stress, DNA damage, and inefficient DNA repair (Weidauer et al., 2004; Dusinska et al., 1998; Ross et al., 1979). Unintentional poisoning episodes in humans have resulted in acute and respiratory effects (Hoppin et al., 2002). Paraquat may also induce delayed health effects including Parkinson's disease and benign lung diseases (Uversky 2004; Wesseling et al., 2001; U.S. Dept. of Agriculture/National Agricultural Statistics Service, 2005). It has been associated with premalignant or malignant skin lesions (Wang et al., 1987), possibly through photosensitivity reaction (Jaworska et al., 1991) and dermal chemical burns (Jee et al., 1995). Excesses of melanoma and leukemia, and cancers of the penis, cervix and lung were observed in a cohort of banana plantation workers, who frequently used paraquat, although only the cervical cancer findings were statistically significant (Wesseling et al., 1996). Another study in Costa Rica assessing cancer incidence in regions with high pesticide use have observed excess overall cancer, skin melanoma, and cancer of the rectum, bladder, ovary, cervix, and lung (Wesseling et al., 1996). The information on potential cancer effects from paraquat exposure is limited and International Association for Research on Cancer (IARC) has not listed paraquat as a potential human carcinogen. Given paraquat's use, further investigation of the cancer risk is warranted. Enrollment (phase I only) data from the Agricultural Health Study was utilized to evaluate cancer risk associated with paraquat use in the cohort

MATERIALS AND METHODS

Cohort recruitment

The AHS is a prospective cohort study of certified pesticide applicators (n=57,311) and their spouses (n=32,347) who were recruited in Iowa and North Carolina between December, 1993 to December, 1997 (Alavanja et al., 1996). Of the eligible licensed applicators 82.4% (n=57,311) enrolled in the study by completing an enrollment questionnaire. Licensed pesticide applicators include private applicators, who are largely farmers, and commercial applicators, from Iowa only, who are employed by pest control and agricultural crop protection companies. Incident cancers diagnosed from enrollment through December 31, 2004 were identified through the cancer registries in Iowa and North Carolina and coded using the *International Classification of Diseases for Oncology* (ICD-O-2) (Percy et al., 1990). A total of 24,665 pesticide applicators (43.9% of the enrolled applicators) provided more detailed information on paraquat use in a take-home questionnaire. This study was approved by Institutional Review Boards at the National Institutes of Health, University of Iowa, Westat Inc., and Battelle. Informed consent was obtained from all participants at the time of enrollment into the Agricultural Health Study.

Exposures and other information

At enrollment, we obtained detailed information on 22 pesticides, including years of use, frequency of use in an average year, and decade when use began, and for 28 additional pesticides, including paraquat, we obtained information on ever versus never use. Information regarding application methods and the use of personal protective equipment was collected for pesticides in general and not for specific pesticides. Participants provided information on possible confounding factors, including tobacco use, alcohol consumption, fruit and vegetable consumption, medical conditions, other agricultural activities, and various non-farm occupational exposures. All participants who completed the enrollment questionnaire were also given a self-administered take-home questionnaire that included

additional questions about exposures, medical conditions, and more detailed questions about the 28 pesticides for which ever versus never use information had been collected in the enrollment questionnaire. All questionnaires are available at www.aghealth.org/questionnaires.

We used two metrics of exposure (lifetime exposure-days and intensity weighted lifetime exposure-days) to characterize paraquat exposure. Lifetime exposure-days (LE) was defined as the number of years a participant personally mixed or applied paraquat times the number of days in an average year that paraquat was used. Intensity-weighted lifetime exposure-days (IWLE) was the product of estimated intensity score of exposure and total LE. The intensity score was calculated as: [(mixing status + application method + equipment repair status) X personal protective equipment used] (Dosemeci et al., 2002). The intensity score heavily weighted the use of protective gloves and thereby dermal exposures and to a lesser extent other protective clothing reflecting our current knowledge of routes of pesticide exposure.

Statistical analysis

Prevalent cancer cases ($n = 1,075$) and two subjects with missing information on date of birth were excluded, leaving 56,222 cohort members in this analysis. Missing data for specific factors were included in the analyses as categorical variables (7.3% of the 56,222 persons were missing information on ever/never use of paraquat; 2.0% and 2.7% of 24,665 subjects with take-home questionnaire were missing information on paraquat LE and IWLE, respectively). We used Poisson regression to calculate rate ratios (RRs) and 95% confidence intervals (CIs). LE and IWLE were categorized into tertiles based on the distribution for all the cancer cases (0.1–7, 7.1–20, 20.1+ for exposure-days and 0.1–36, 36.1–154, 154.1+ for intensity-weighted exposure-days).

Two reference groups were used for the analyses: pesticide applicators who reported never using paraquat and pesticide applicators whose use of paraquat was in the lowest tertile of exposure. Models were adjusted for age at enrollment (< 40, 40–49, 50–59, 60 years), education (high school graduate, > high school graduate), cigarette smoking (by pack-years: never, 14, > 14), alcohol consumption during the last 12 months (yes/no), family history of cancer (yes/no), research site (Iowa/North Carolina), and the five pesticides with the highest correlation coefficients with paraquat exposure by IWLE [metribuzin, pendimethalin, Silvex (2,4,5-TP), butylate, and dieldrin]. The correlation coefficients for these five pesticides were small and ranged between 0.30 (pendimethalin) and 0.34 (metribuzin). Linear trends for RR were assessed using the median value for each tertile of exposure in the models, adjusting for covariates. If the sample size in a category for analysis was five or fewer, we combined subjects in the middle and lowest tertiles of LE and IWLE resulting in two categories (0.1–20, 20.1+ exposure-days; 0.1–154, 154.1+ intensity-weighted exposure-days). For colon, lung and NHL analyses, we combined subjects in middle and lowest tertiles of LE and IWLE, since the number of exposed subjects in the middle tertile group was small ($n=2$).

The AHS data release version used was “REL0612” (enrollment or phase I data only). All analyses were conducted using SAS version 9.1.

RESULTS

Among the 56,222 private and commercial applicators, 20.0% ($n=11,256$) reported having ever used paraquat, 72.7% ($n=40,861$) reported having never used paraquat and 7.3% ($n=4,105$) did not report on paraquat use (Table 1). The subjects with no information for paraquat exposure were older than the subjects in other categories. Follow-up time and the distribution of gender and race were similar among the non-exposed group and exposed groups. Iowa applicators were less likely to report paraquat use than subjects from North

Carolina. The median follow-up time for all subjects was 7.8 years. Commercial applicators were more common among the exposed groups. Of the 50 pesticides, the five most highly correlated with paraquat use were metribuzin, pendimethalin, silvex (2,4,5-TP), butylate, and dieldrin.

The rate ratios (RRs) of selected cancers among AHS applicators are shown in Table 2. Ever use of paraquat was not associated with cancer incidence overall, or most individual cancers. It was associated with non-Hodgkin's lymphoma (NHL) (RR [95% CI] = 1.51 [1.01–2.26]). There was a non-significant excess risk of leukemia and pancreatic cancer among paraquat users (RR= 1.36 [0.72–2.58]; RR= 1.66 [0.79–3.49], respectively). Paraquat use was not significantly associated with lung, kidney, bladder, and female breast cancers, or skin melanoma.

The RRs for selected cancers by the LE and IWLE paraquat exposure metrics among 24,665 subjects who returned a take-home questionnaire are presented in Table 3. Compared to participants with no reported paraquat use, those in the middle tertile and highest tertile of paraquat exposure level had an increased risk of NHL. However the RRs were not statistically significant (RR=1.18 [0.51–2.71], RR [95% CI] = 1.74 [0.69–4.42] for LE; and RR=1.25 [0.57–2.78], 1.86 [0.68–5.11] for IWLE, respectively), nor were the exposure-response trends for either LE or IWLE (p-trend=0.232; 0.197, respectively). However, the number of NHL cases in the exposed groups was small due to the limited number of follow-up years. In analyses using the low exposed group as the reference, the increased risks for NHL (RR=1.23 [0.40–3.74] for highest tertile of LE; 1.15 [0.36–3.62] for highest tertile of IWLE) were not statistically significant. The RRs for prostate, lung and colon cancers were not consistent across exposure categories. Paraquat LE or IWLE was not associated with any other cancers for which we had sufficient numbers of cases to explore risk.

DISCUSSION

In this study, NHL risk was significantly associated with the ever-use of paraquat. Monotonic but non-significant trends of increasing risk were observed for increasing lifetime exposure days and intensity weighted lifetime exposure days using non-exposed for comparison, but not when using low exposed as the referent. None of the exposure-response trends were statistically significant.

Previous studies of workers employed in the production of paraquat or farmers living in coffee growing areas where paraquat is extensively used were found to be at higher risk of developing skin melanoma, and cancer of the rectum, bladder, ovary, cervix, and lung (Wesseling et al., 1996), but not non-Hodgkin's lymphoma. We found no excesses for the cancers noted in earlier studies. Our knowledge about the possible mechanism of action of paraquat in human carcinogenesis is limited. The occurrence of chromosomal aberrations and gene mutations in human lymphocytes exposed to paraquat in vitro is interesting (Salam et al., 1993; Kuo et al., 1993; Rios et al., 1995; Ribas et al., 1997/98), given the suggestion of an association with NHL in our data. Further investigation of the association between paraquat and NHL is warranted as more cases occur in the AHS cohort and elsewhere.

Several limitations of this study should be noted. Despite being the largest cohort study of the association between NHL and paraquat to date, the number of exposed incident cancers is small and the follow-up interval is relatively short at this time. Pesticide exposure patterns can be complex and the use of several pesticides may be correlated. While we were able to control for the use of other pesticides in our analyses and saw no change in cancer risk estimates with these adjustments, the precision of our estimates was limited. Although farmers can provide considerable detail on their pesticide use (Blair & Zahm 1995) and the

reliability of reporting in the study is quite good (Blair 2002; Hoppin 2002), some misclassification of exposures also undoubtedly occurred. In a prospective study, such misclassification of exposure is likely to be nondifferential, which would tend to bias estimates of relative risk toward the null.

The strengths of this study include its prospective design, thereby minimizing the potential for recall bias and ensuring temporal relevance of any associations uncovered between paraquat exposure and cancer, and detailed information on the use of many different pesticides. Availability of comprehensive information collected about other jobs, medical conditions and lifestyle factors also allowed adjustment for many potential confounders.

Continued updating of paraquat exposure and accumulation of more incident cases will allow for future re-evaluation.

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Table 1
Selected characteristics of pesticide applicators by lifetime exposure-days (LE) to paraquat in the AHS (n=56,222)

	Missing paraquat exposure ^I (n=4,105)		Non-exposed ^I (n=40,861)		Low-exposed Lowest tertile ² (n=916)		Exposed ^I High-exposed High two tertiles ² (n=3,012)		Exposed but missing LE ^I & ² (n=7,328)	
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)
Age										
<40	971 (23.7)	13757 (33.6)	252 (27.5)	776 (25.8)	2466 (33.6)					
40-49	765 (18.6)	11315 (27.7)	249 (27.1)	878 (29.2)	2263 (30.9)					
50-59	956 (23.3)	8243 (20.2)	214 (23.4)	673 (22.3)	1516 (20.7)					
>=60	1413 (34.4)	7546 (18.5)	201 (21.9)	685 (22.7)	1083 (14.8)					
Gender										
Male	3918 (95.5)	39634 (97.0)	905 (98.8)	2977 (98.9)	7247 (98.9)					
Female	187 (4.5)	1227 (3.0)	11 (1.2)	35 (1.2)	81 (1.1)					
Race										
White	3027 (73.8)	39449 (96.5)	879 (96.0)	2879 (95.6)	7126 (97.3)					
Non White	395 (9.6)	885 (2.2)	11 (1.2)	30 (1.0)	177 (2.4)					
Missing	683 (16.6)	527 (1.3)	26 (2.8)	103 (3.4)	25 (0.3)					
State										
Iowa	1184 (28.8)	30740 (75.2)	531 (58.0)	940 (31.2)	2644 (36.1)					
North Carolina	2921 (71.2)	10121 (24.8)	385 (42.0)	2072 (68.8)	4684 (63.9)					
Applicator type										
Farmer ^I	3990 (97.2)	37248 (91.2)	797 (87.0)	2609 (86.6)	6711 (91.6)					
Commercial	115 (2.8)	3613 (8.8)	119 (13.0)	403 (13.4)	617 (8.4)					
Education										
<=High school	3287 (80.0)	23913 (58.5)	475 (51.9)	1525 (50.6)	3970 (54.2)					
> High school	808 (19.7)	16855 (41.3)	439 (47.9)	1482 (49.2)	3341 (45.6)					
Missing	10 (0.3)	93 (0.2)	2 (0.2)	5 (0.2)	17 (0.2)					
Smoking										
Never	1335 (32.5)	22207 (54.3)	428 (46.7)	1348 (44.7)	3445 (47.0)					
Ex	1181 (28.8)	11717 (28.7)	319 (34.8)	1038 (34.5)	2261 (30.8)					
Current	710 (17.3)	6296 (15.4)	143 (15.6)	512 (17.0)	1587 (21.7)					

	Missing paraquat exposure ^I (n=4,105)	Non-exposed ^I (n=40,861)		Low-exposed Lowest tertile ² (n=916)		Exposed ^I High-exposed High two tertiles ² (n=3,012)		Exposed but missing LE ^I & 2 (n=7,328)
		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Missing	879 (21.4)	641 (1.6)	26 (2.8)	114 (3.8)	35 (0.5)			
Alcohol use								
No	1004 (24.5)	11863 (29.0)	292 (31.9)	1157 (38.4)	2701 (36.9)			
Yes	916 (22.3)	27888 (68.3)	586 (64.0)	1691 (56.1)	4529 (61.8)			
Missing	2185 (53.2)	1110 (2.7)	38 (4.1)	164 (5.5)	98 (1.3)			
Family history of cancer								
No	922 (22.4)	22959 (56.2)	454 (49.6)	1517 (50.4)	4004 (54.6)			
Yes	431 (10.5)	15043 (36.8)	377 (41.2)	1184 (39.3)	2783 (38.0)			
Missing	2752 (67.1)	2859 (7.0)	85 (9.2)	311 (10.3)	541 (7.4)			
Corn production								
No	2470 (60.2)	10482 (25.6)	312 (34.1)	1242 (41.2)	2527 (34.5)			
Yes	1635 (39.8)	30379 (74.4)	604 (65.9)	1770 (58.8)	4801 (65.5)			
Take-home questionnaire								
No	3846 (93.7)	20623 (50.5)	0 (0.0)	0 (0.0)	7088 (96.7)			
Yes	259 (6.3)	20238 (49.5)	916 (100.0)	3012 (100.0)	240 (3.3)			
Other pesticide use Merribuzin								
No	12 (0.3)	12952 (45.8)	489 (53.4)	1601 (53.3)	76 (1.0)			
Yes	5 (0.1)	6682 (2.2)	401 (43.7)	1289 (42.8)	35 (0.5)			
Missing	4088 (99.7)	21227 (52.0)	26 (2.9)	118 (3.9)	7217 (98.5)			
Pendimethalin								
No	36 (0.9)	13035 (31.9)	439 (47.9)	1299 (43.1)	74 (1.0)			
Yes	28 (0.7)	6471 (15.8)	453 (49.5)	1611 (53.5)	56 (0.8)			
Missing	4041 (98.4)	21355 (52.3)	24 (2.6)	102 (3.4)	7198 (98.2)			
Silvex (2,4,5-TP)								
No	33 (0.8)	18997 (46.5)	835 (91.2)	2564 (85.1)	121 (1.7)			
Yes	1 (0.0)	684 (1.7)	59 (6.4)	354 (11.8)	8 (0.1)			
Missing	4071 (99.2)	21180 (51.8)	22 (2.4)	94 (3.1)	7199 (98.2)			
Butylate								
No	26 (0.6)	15105 (37.0)	590 (64.4)	1036 (62.0)	97 (1.3)			

	Missing paraquat exposure ¹ (n=4,105)	Non-exposed ¹ (n=40,861)		Low-exposed Lowest tertile ² (n=916)		Exposed ¹ High-exposed High two tertiles ² (n=3,012)		Exposed but missing LE ¹ & ² (n=7,328)
		No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Yes	6 (0.2)	4538 (11.1)	306 (33.4)	1868 (34.4)	33 (0.5)			
Missing	4073 (99.2)	21218 (51.9)	20 (2.2)	108 (3.6)	7198 (98.2)			
Dieldrin								
No	54 (1.3)	19069 (46.7)	846 (92.4)	2766 (91.8)	142 (1.9)			
Yes	2 (0.1)	572 (1.4)	43 (4.7)	151 (5.0)	7 (0.1)			
Missing	4049 (98.6)	21220 (51.9)	27 (2.9)	95 (3.2)	7179 (98.0)			

¹ based on enrollment questionnaire

² based on the take-home questionnaire only

Table 2

Rate ratios for selected cancers, by exposure status to paraquat among AHS applicators

	Total subjects (n=56,222)		Subjects who returned a take home questionnaire (n=24,665)	
	N of cases	RR (95% CI) ¹	N of cases	RR (95% CI) ¹
All Cancers				
Non-exposed	2,441	1.00 (reference)	1,459	1.00 (reference)
Exposed	667	0.96 (0.88–1.05)	306	0.99 (0.86–1.13)
Prostate cancer				
Non-exposed	1,002	1.00 (reference)	625	1.00 (reference)
Exposed	252	0.96 (0.83–1.18)	122	0.95 (0.77–1.18)
Lung cancer				
Non-exposed	221	1.00 (reference)	137	1.00 (reference)
Exposed	85	1.09 (0.83–1.43)	33	0.95 (0.63–1.43)
Colon cancer				
Non-exposed	193	1.00 (reference)	112	1.00 (reference)
Exposed	46	0.89 (0.63–1.25)	25	1.32 (0.82–2.13)
Pancreas cancer				
Non-exposed	38	1.00 (reference)	21	1.00 (reference)
Exposed	14	1.66 (0.79–3.49)	7	1.52 (0.6–3.76) ²
Kidney cancer				
Non-exposed	67	1.00 (reference)	37	1.00 (reference)
Exposed	20	0.99 (0.58–1.71)	9	1.08 (0.48–2.42)
Bladder cancer				
Non-exposed	105	1.00 (reference)	64	1.00 (reference)
Exposed	25	0.92 (0.57–1.49)	12	0.95 (0.48–1.90)
Non-Hodgkin's lymphoma				
Non-exposed	95	1.00 (reference)	47	1.00 (reference)
Exposed	41	1.51 (1.01–2.26)**	18	1.72 (0.94–3.18)*
Leukemia				
Non-exposed	77	1.00 (reference)	45	1.00 (reference)
Exposed	19	1.36 (0.72–2.58)	11	1.41 (0.70–2.84) ²
Skin melanoma				
Non-exposed	88	1.00 (reference)	56	1.00 (reference)
Exposed	23	0.94 (0.58–1.52) ²	13	1.02 (0.54–1.02) ²

*, 0.05 p<0.1,

**
p 0.05¹ Adjusted for age at enrollment, education, research site, cigarette smoking, alcohol consumption, family history of cancers, and 5 pesticides correlated with paraquat² Adjusted for age at enrollment, education, research site, cigarette smoking, alcohol consumption, and family history of cancers. The 5 pesticides correlated with paraquat were not included in the adjustment because the mean parameter was either invalid or at a limit of its range for some observations due to the small number of cancer cases

Table 3

Rate ratios for selected cancers by lifetime exposure-days (LE) and intensity weighted lifetime exposure-days (IWLE) to paraquat among AHS applicators with non-exposed and low exposed as referent groups, among 24,665 subjects who returned a take-home questionnaire

	Lifetime exposure-days (LE)			Intensity weighted lifetime exposure-days (IWLE)		
	N of cases	Non-exposed referent 1 RR _{LE} (95% CI) ¹	Low-exposed referent RR _{LE} (95% CI) ¹	N of cases ³	Non-exposed referent RR _{IWLE} (95% CI) ¹	Low-exposed referent 1 RR _{IWLE} (95% CI) ¹
All Cancer						
Non-exposed	1459	1.00 (reference)		1459	1.00 (reference)	
0.1-7	69	1.07(0.84-1.37)	1.00 (reference)	88	1.04 (0.84-1.29)	1.00 (reference)
7.1-20.0	101	0.94(0.76-1.15)	0.87 (0.63-1.19)	90	0.99 (0.80-1.24)	0.94 (0.70-1.27)
20.1+	110	0.98(0.80-1.21)	0.91 (0.66-1.26)	90	0.95 (0.76-1.20)	0.91 (0.66-1.24)
	<i>P-trend</i> §	0.757	0.653		0.805	0.550
Prostate						
Non-exposed	625	1.00 (reference)		625	1.00 (reference)	
0.1-7	35	1.27(0.90-1.80)	1.00 (reference)	42	1.16(0.84-1.60)	1.00 (reference)
7.1-20.0	38	0.85(0.61-1.19)	0.65 (0.41-1.04)	34	0.90(0.63-1.28)	0.76(0.48-1.21)
20.1+	38	0.83(0.59-1.18)	0.61 (0.35-1.02)	32	0.83(0.57-1.20)	0.68(0.41-1.11)
	<i>P-trend</i> §	0.303	0.069		0.396	0.116
Lung						
Non-exposed	137	1.00 (reference)		137	1.00 (reference)	
0.1-24.5	21	1.08(0.67-1.74)	1.00 (reference)	19	1.02(0.62-1.69)	1.00 (reference)
24.5+	11	0.83(0.43-1.59)	0.76 (0.35-1.62)	10	0.92(0.46-1.83)	0.91(0.41-2.05)
	<i>P-trend</i> §	0.659	-		0.799	-
Colon						
Non-exposed	112	1.00 (reference)		112	1.00 (reference)	
0.1-20.0	18	1.68(0.99-2.84)	1.00 (reference)	15	1.42(0.80-2.50)	1.00 (reference)
20.1+	6	0.96(0.41-2.28)	0.56 (0.22-1.42) ²	7	1.35(0.60-3.05)	0.95(0.38-2.40) ²
	<i>P-trend</i> §	0.481	-		0.238	
Non-Hodgkin's lymphoma						
Non-exposed	47	1.00 (reference)		47	1.00 (reference)	
0.1-20.0	7	1.18(0.51-2.71)	1.00 (reference)	8	1.25(0.57-2.78)	1.00 (reference)

	Lifetime exposure-days (LE)			Intensity weighted lifetime exposure-days (IWLE)		
	Non-exposed referent 1		Low-exposed referent	Non-exposed referent		Low-exposed referent 1
	N of cases	RR _{LE} (95% CI) ¹		RR _{IWLE} (95% CI) ¹	N of cases ³	RR _{IWLE} (95% CI) ¹
20,1+	6	1.74 (0.69–4.42)	1.23 (0.40–3.74) ²	154,1+	5	1.15 (0.36–3.62) ²
	<i>P-trend</i> §	0.232	-	<i>P-trend</i> §	0.197	-

P-trend§, P-values for trend among the subjects with information of life duration.

¹ Adjusted for age at enrollment, education, research site, cigarette smoking, alcohol consumption, family history of cancers, and 5 pesticides correlated with paraquat

² Adjusted for age at enrollment, education, research site, cigarette smoking, alcohol consumption, and family history of cancers. The 5 pesticides correlated with paraquat were not included in the adjustment because the mean parameter was either invalid or at a limit of its range for some observations due to the small number of cancer cases.

³ Numbers do not always sum to those of lifetime exposure-days due to missing data