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Cancer incidence among pesticide applicators exposed to trifluralin in the Agricultural Health Study

Daehee Kang^{1,2}, Sue Kyung Park², Laura Beane-Freeman¹, Charles F. Lynch³, Charles E. Knott⁴, Dale P. Sandler⁵, Jane A. Hoppin⁵, Mustafa Dosemeci¹, Joseph Coble¹, Jay Lubin¹, Aaron Blair¹, Michael Alavanja¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, DHHS

²Seoul National University College of Medicine, Korea

³Department of Epidemiology, University of Iowa

⁴Battelle Centers for Public Health Research and Evaluation

⁵Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, DHHS

Abstract

Trifluralin, 2,6-dinitro-N,N-dipropyl-4-trifluoromethylaniline, is a 2,6-dinitro herbicide widely used to control annual grasses and broadleaf weeds in agricultural settings. The association between trifluralin use and common cancer incidence was evaluated among 50,127 private and commercial pesticide applicators in the Agricultural Health Study (AHS), a prospective cohort study of licensed pesticide applicators and their spouses in Iowa and North Carolina. Poisson regression was used to examine internal dose-response relationships, while controlling for important lifestyle factors and other agricultural exposures. Two metrics of exposure (lifetime days and intensity-weighted lifetime days) were used in exposure-response analyses with non-exposed applicators, as well as applicators in the lowest tertile of exposure, as reference groups. Incident cancers were identified through state tumor registries from enrollment in 1993 through 2002. Trifluralin exposure was not associated with cancer incidence overall among 51% of private and commercial applicators (n=25,712) who had used trifluralin. However, there was an excess of colon cancer in the exposure category of higher half of highest tertile (rate ratios (RR) of 1.76 (95% CI=1.05-2.95) using the non-exposed as a referent and 1.93 (95% CI=1.08-3.45) using those with the lowest tertile of exposure as the referent). There was also a non-significantly elevated risk for kidney cancer and bladder cancer in the highest exposure group, although only the kidney cancer finding was consistent across exposure metrics. Although there was a possible link between trifluralin exposure and colon cancer, small numbers and inconsistencies in dose response and subgroup analyses indicate that this may be a chance finding.

Keywords

agriculture; trifluralin; pesticides; cancer; occupational exposure

Introduction

Trifluralin, 2,6-dinitro-N,N-dipropyl-4-trifluoromethylaniline, is a 2,6-dinitro herbicide widely used to control annual grasses and broadleaf weeds in agricultural settings.¹ Of the 24,000 tons produced worldwide in 1998, about 64% was used on soybeans, and 19% was used on cotton (<http://www.panuk.org/pestnews/Actives/Triflura.htm>). Trifluralin has also been detected in non-occupational settings. Of the five most commonly used herbicides in the Canadian Prairies, it was most frequently detected in air (79% of samples).² It was also the most frequently detected pesticide on the hands (60%) for 14 pesticides measured among 20 non-occupationally exposed adults in France.³

There are a number of reports evaluating trifluralin for genotoxicity. Although the results are not entirely consistent, trifluralin does not appear to be strongly genotoxic.⁴ The wing spot test of *Drosophila matanogaster* (somatic mutation and recombination test) showed positive results with both standard and high-bioactivation strains.⁵ Trifluralin caused a significant increase in the number of micronuclei from the *in vivo* genotoxicity test in female mouse bone-marrow cells⁶ but not in cultured human peripheral blood lymphocytes.⁷ Trifluralin increased the comet tail lengths in the single-cell gel electrophoresis (SCGE) assay.⁸ It did not affect the immune function in male Fisher 344 rats,⁹ but did appear to influence serum concentrations of reproductive and metabolic hormones, particularly thyroxine.¹⁰

Trifluralin is considered as possible human carcinogen by EPA based on the induction of urinary tract tumors and thyroid tumors in rats.^{1,11} Few epidemiologic studies of trifluralin have been conducted. A significant excess risk (OR=12.5, 95% CI=1.6116.1) of non-Hodgkin's lymphoma (NHL) was associated with ever use of trifluralin in a small case-control study (only three patients of total 170 NHL cases and 2 of 948 controls had reported to use trifluralin),¹² but a recent pooled analysis (870 NHL cases and 2,569 controls) found no association (OR=0.9, 95% CI=0.5-1.6).¹³

No prospective epidemiologic studies with cancer outcomes from trifluralin exposure have ever been reported. Thus, the Agricultural Health Study, a prospective cohort study, was used to evaluate the relationship between trifluralin and cancer incidence.

Method

Cohort enrollment and follow-up

The Agricultural Health Study (AHS) is a prospective cohort study of 57,311 private and commercial pesticide applicators licensed to apply restricted-use pesticides in Iowa and North Carolina. Recruitment of the applicators occurred between 1993 and 1997.¹⁴ Cohort members are 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 through state cancer registries from enrollment in

1993 through 2002. If cohort members had moved from the state, they were censored in the year they left. The mean time of follow-up was 7.43 (standard deviation=1.49) years.

Exposure assessment

A self-administered enrollment questionnaire provided comprehensive exposure data on 22 pesticides including trifluralin and information on ever/never use for 28 additional pesticides, use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, smoking history, alcohol consumption, cancer history of first-degree relatives, diet, medical history, and other basic demographics.¹⁵ Applicators completing the enrollment questionnaire were given a self-administered take-home questionnaire, which contained additional questions on occupational exposures and lifestyle factors.

Two metrics of exposure (lifetime days and intensity-weighted lifetime days) were used in exposure-response analyses. Lifetime days or 'cumulative exposure days' (years of use X days per year) were categorized in tertiles at 4 levels [lower two tertiles, and lower and higher half of highest tertile] among users: 1-24.4, 24.5-108.4, 108.5-224.75, >224.75). Intensity-weighted lifetime days (IWLD, years of use X days per year X intensity levels) were also categorized in tertiles at 4 levels: 0-162.1, 162.2-593, 593.1-1176.0, >1176.0). Exposure intensity levels were estimated using information from the enrollment questionnaire and a pesticide exposure algorithm where: intensity level = [(mixing status + application method + equipment repair status) X personal protective equipment use], with weights for these variables derived from the published literature.¹⁶

Data analysis

Prevalent cancer cases (n=1,075) identified prior to the time of enrollment, and cases who did not provide information on trifluralin use (n=6,107) or age (n=2) were excluded, leaving 50,127 applicators in this analysis.

We used two different referent groups, i.e., applicators never exposed to trifluralin and applicators exposed to trifluralin in the lowest exposure tertile, because they have slightly different characteristics and it is not entirely clear which is the most appropriate for comparison. We compared the baseline characteristics of: 1) applicators never exposed to trifluralin, 2) applicators with trifluralin exposure in the lowest tertile of lifetime days of exposure, and 3) applicators with trifluralin exposure in the highest two tertiles of lifetime days of exposure.

Poisson regression was used to estimate rate ratios (RRs) and 95% confidence interval (CIs) associated with trifluralin exposure metrics using non-exposed applicators, as well as those in the lowest tertile of exposure, as the reference group. RRs were adjusted for demographic and lifestyle factors, including age at enrollment (<40, 40-49, 50-59, >60), education (<=high school graduate or beyond high school), cigarette smoking (ever/never), alcohol consumption in the past year (ever/never), family history of cancer in first-degree relatives (yes/no), state of residence (Iowa/North Carolina), and the top five pesticides for which lifetime days of exposure were most highly correlated with trifluralin exposure (dicamba, metolachlor, imazethapyr, metribuzin, cyanazine) (Table 1). A test for trend was conducted

using assigned values equal to the median value of lifetime days (or intensity-weighted lifetime days) for each level of trifluralin exposure.

Results

Among private and commercial applicators, 51% (n=25,712) reported having ever used trifluralin (Table I). Non-exposed and exposed (lower and higher groups cut at the median) are compared for various demographic and exposure characteristics in Table 1. Those in the higher exposure categories were more likely to be men, reside in Iowa, and have some education beyond high school (Table I).

Trifluralin exposure was not associated with cancer incidence overall, or with most individual cancer sites (Table II). There was an excess of colon cancer in the upper level of the highest tertile of intensity-weighted lifetime days (RR=1.76 (95% CI=1.05-2.95, $P_{\text{trend}}=0.036$) using the non-exposed as a referent; RR=1.93 (95% CI=1.08-3.45, $P_{\text{trend}}=0.037$) using those with the lowest tertile of exposure as the referent). Although the tests for trend were statistically significant, neither displayed a clear dose-response. The relationship between colon cancer and lifetime exposure-days was weaker than for intensity-weighted lifetime days. There were no statistically significant associations with right-sided or left-sided colon cancers and no differences by state.

There were non-significant excesses of bladder cancer and kidney cancer in the highest exposure category, particularly for the lifetime days exposure metric, but these are based on small numbers.

Discussion

There was no association between trifluralin exposure and all cancer incidence or most of the specific cancer subtypes we evaluated. The statistically significant association with colon cancer has not been previously reported, but also did not show a clear dose response or any preference for right or left colon. Results were similar for state-specific analyses. Although a few studies have observed an increased risk of colon cancer associated with farming occupation and/or herbicide exposure,¹⁷⁻¹⁹ the relative risk for colon cancer has often been reduced in meta-analyses of farmers.^{20,21} In a previous analysis of colon cancer in the AHS,²² no association was observed between trifluralin and colon cancer when compared between never and ever users. Our finding was not significant either when categorized into never and ever users (RR=1.01, 95% CI=0.76-1.61). The difference in results might be due to use of different exposure cut-points. In the chemical specific analysis used in this paper, the tertiles were based on total number of cancer cases, but in the colon cancer specific analysis the tertiles were based on specific pesticide use by colorectal cancer cases. The instability in the risk estimate for colon cancer and trifluralin exposure using different cut points suggests that the association observed here could be a chance finding.

Bioassays have reported the occurrence of bladder and kidney cancers in rats exposed to trifluralin,¹ but we saw no significant excesses for these tumors. The relative risks of bladder and kidney cancer were slightly elevated in the highest exposure category, but the variation by exposure metric and small numbers suggest these may also be chance findings.

Bioassay and experimental studies have suggested that trifluralin inhibits the induction of lung and forestomach cancers in mice treated with benzo(a)pyrene.²³ We saw no evidence of such a lung cancer reduction among individuals exposed to trifluralin in this cohort.

The Agricultural Health Study has a number of strengths. First, it is the largest prospective study of pesticide applicators exposed to trifluralin that has been conducted to date. Second, detailed exposure information was collected before the diagnosis of cancer, which eliminates recall bias. Third, information on duration, frequency and intensity of use of agricultural pesticides was obtained, which provided the opportunity to relate quantitative estimates of exposure to cancer risk. Fourth, information was obtained on a large number of agricultural exposures and lifestyle factors, which allows careful adjustment for possible confounding. Fifth, although the study relied on self-reported exposure information, study subjects provided reliable information regarding their personal pesticide use.^{24,25} Finally, the outcome is cancer incidence.

This study also has limitations. Although quantitative estimates of exposure to trifluralin and other pesticides were developed, undoubtedly exposure misclassification exists. In a prospective study, exposure misclassification would be nondifferential which would tend to move estimates of relative risks toward the null and flatten exposure-outcome relationships.^{26,27} Although the Agricultural Health Study has a large number of subjects, the small number of specific cancers occurring during the 7.4 years of average follow-up prevented estimation of precise effects.

In this prospective evaluation of cancer risk, trifluralin was not associated with most cancers. There was some suggestion of a possible link between trifluralin exposure and colon cancer risk in humans, but the inconsistency by exposure level and small numbers of colon cancers indicate this could be a chance finding.

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Table I

Selected characteristics of applicators, by trifluralin exposure in the Agricultural Health Study between 1993-1997 (n=50,127)

Characteristics	Non-exposed (n=24,415) No. (%)	Low-exposed (n=8,509) No. (%)	High-exposed (n=17,203) No. (%)
Age ^I			
<40	8,699 (35.6)	2,945 (34.6)	5,222 (30.4)
40-49	6,398 (26.2)	2,340 (27.5)	5,557 (32.3)
50-59	4,684 (19.2)	1,742 (20.5)	3,710 (21.6)
>=60	4,633 (19.0)	1,482 (17.4)	2,713 (15.8)
Sex			
Male	23,366 (95.7)	8,381 (98.5)	17,087 (99.3)
Female	1049 (4.3)	128 (1.5)	116 (0.7)
State of residence			
Iowa	13,295 (54.4)	6,395 (75.2)	14,543 (84.5)
North Carolina	11,120 (45.6)	2,114 (24.8)	2,660 (15.5)
Applicator type			
Private	21,949 (89.9)	8,089 (95.1)	15,491 (90.5)
Commercial	2,466 (10.1)	420 (4.9)	1,712 (9.5)
Education ^I			
High school graduate	14,651 (60.2)	4,512 (53.2)	9,193 (53.5)
Beyond high school	9,692 (39.8)	3,975 (46.8)	7,989 (46.5)
Smoking ^I			
Never	12,677 (52.5)	4,754 (56.1)	9,309 (54.3)
Former	7,124 (29.5)	2,459 (29.0)	5,147 (30.0)
Current	4,351 (18.0)	1,264 (14.9)	2,695 (15.7)
Alcohol use ^I			
No	8,679 (36.4)	2,402 (28.7)	4,167 (24.6)
Yes	15,139 (63.6)	5,969 (71.3)	12,761 (75.4)
Family history of cancer ^I			
No	14,162 (62.7)	4,673 (58.3)	9,264 (57.0)
Yes	8,627 (37.3)	3,338 (41.7)	6,999 (43.0)
Use of other pesticides highly correlated with trifluralin			
Dicamba	7,570 (32.0)	4,711 (57.4)	11,973 (71.8)
Metolachlor	6,253 (26.1)	4,695 (56.8)	11,544 (69.1)
Imazethayr	5,057 (21.3)	4,320 (52.8)	11,299 (67.9)
Metribuzin	1,570 (15.2)	1,729 (46.0)	5,044 (65.4)
Cyanazine	6,701 (23.8)	4,090 (49.7)	10,236 (61.3)

^I Numbers do not always sum to total because of missing data.

Table II

Association of trifluralin exposure (lifetime exposure-days (LD) and intensity-weighted lifetime exposure-days (IWLD) with common cancers among Agricultural Health Study applicators

Cancer site	N	RR _{LD} (95% CI) ^I	N	RR _{LD} (95% CI) ^I	N	RR _{IWLD} (95% CI) ^I	N	RR _{IWLD} (95% CI) ^I
All Cancer								
Nonexposed	1,160	1.00 (reference)			1,160	1.00 (reference)		
T1	345	0.92 (0.81-1.04)	345	1.00 (reference)	348	0.90 (0.79-1.02)	348	1.00 (reference)
T2	396	0.94 (0.83-1.07)	396	1.01 (0.88-1.17)	347	0.99 (0.87-1.13)	347	1.09 (0.94-1.27)
T3 _L	216	1.13 (0.97-1.32)	216	1.22 (1.03-1.45)	177	1.01 (0.85-1.20)	177	1.11 (0.93-1.34)
T3 _U	110	0.90 (0.73-1.10)	110	0.95 (0.76-1.19)	179	0.99 (0.83-1.17)	179	1.08 (0.90-1.30)
P _{trend}		0.844		0.673		0.729		0.522
Prostate								
Nonexposed	452	1.00 (reference)			452	1.00 (reference)		
T1	132	0.83 (0.68-1.02)	132	1.00 (reference)	134	0.81 (0.66-0.99)	134	1.00 (reference)
T2	177	0.97 (0.79-1.18)	177	1.13 (0.90-1.43)	151	1.01 (0.82-1.23)	151	1.23 (0.97-1.55)
T3 _L	98	1.22 (0.96-1.54)	98	1.42 (1.09-1.86)	75	1.01 (0.78-1.31)	75	1.21 (0.91-1.61)
T3 _U	33	0.64 (0.45-0.94)	33	0.74 (0.50-1.09)	74	0.98 (0.76-1.28)	74	1.18 (0.89-1.57)
P _{trend}		0.443		0.487		0.674		0.499
Lung								
Nonexposed	121	1.00 (reference)			121	1.00 (reference)		
T1	37	1.27 (0.86-1.88)	37	1.00 (reference)	39	1.36 (0.92-2.01)	39	1.00 (reference)
T2	23	0.85 (0.53-1.40)	23	0.68 (0.40-1.16)	18	0.77 (0.45-1.30)	18	0.57 (0.32-1.00)
T3 _L	20	1.54 (0.91-2.59)	20	1.22 (0.70-2.15)	16	1.37 (0.78-2.40)	16	1.04 (0.58-1.89)
T3 _U	12	1.29 (0.68-2.46)	12	1.02 (0.51-2.03)	17	1.30 (0.75-2.25)	17	0.96 (0.54-1.73)
P _{trend}		0.261		0.471		0.365		0.602
Lymphatic-hematopoietic cancers								
Nonexposed	116	1.00 (reference)			116	1.00 (reference)		
T1	34	0.80 (0.53-1.20)	34	1.00 (reference)	31	0.71 (0.47-1.08)	31	1.00 (reference)
T2	43	0.89 (0.60-1.33)	43	1.11 (0.70-1.75)	39	0.96 (0.14-1.45)	39	1.35 (0.84-2.18)
T3 _L	18	0.81 (0.48-1.38)	18	1.01 (0.57-1.80)	20	0.98 (0.59-1.64)	20	1.37 (0.77-2.42)
T3 _U	11	0.79 (0.41-1.53)	11	0.93 (0.46-1.88)	12	0.57 (0.31-1.07)	12	0.78 (0.40-1.53)
P _{trend}		0.548		0.775		0.211		0.319
NHL								
Nonexposed	53	1.00 (reference)			53	1.00 (reference)		
T1	17	0.86 (0.48-1.53)	17	1.00 (reference)	15	0.74 (0.40-1.36)	15	1.00 (reference)
T2	23	1.03 (0.59-1.80)	23	1.31 (0.69-2.49)	20	1.06 (0.80-1.89)	20	1.51 (0.77-2.97)
T3 _L	6	0.56 (0.23-1.37)	6	0.72 (0.28-1.84)	9	0.93 (0.43-1.99)	9	1.34 (0.58-3.08)
T3 _U	4	0.58 (0.20-1.69)	4	0.73 (0.23-2.15)	4	0.39 (0.14-1.14)	4	0.56 (0.18-1.70)
P _{trend}		0.186		0.292		0.137		0.223
Leukemia								

Cancer site	N	RR _{LD} (95% CI) ^I	N	RR _{LD} (95% CI) ^I	N	RR _{IWLD} (95% CI) ^I	N	RR _{IWLD} (95% CI) ^I
Nonexposed	38	1.00 (reference)			38	1.00 (reference)		
T1	10	0.69 (0.33-1.65)	10	1.00 (reference)	8	0.53 (0.24-1.19)	8	1.00 (reference)
T2	12	0.71 (0.34-1.47)	12	0.93 (0.40-2.18)	12	0.87 (0.42-1.79)	12	1.53 (0.62-3.77)
T3 _L	9	1.19 (0.53-2.67)	9	1.53 (0.61-3.84)	8	1.16 (0.50-2.68)	8	1.96 (0.72-5.28)
T3 _U	3	0.61 (0.18-2.13)	3	0.67 (0.17-2.56)	5	0.70 (0.26-1.90)	5	1.13 (0.36-3.52)
P _{trend}		0.929		0.899		0.91		0.999
Colon								
Nonexposed	85	1.00 (reference)			85	1.00 (reference)		
T1	25	0.93 (0.58-1.48)	25	1.00 (reference)	25	0.90 (0.56-1.44)	25	1.00 (reference)
T2	29	0.94 (0.59-1.51)	29	0.96 (0.55-1.65)	29	1.14 (0.71-1.82)	29	1.23 (0.72-2.12)
T3 _L	18	1.30 (0.74-2.26)	18	1.35 (0.73-2.50)	8	0.63 (0.30-1.35)	8	0.69 (0.31-1.54)
T3 _U	13	1.48 (0.78-2.80)	13	1.50 (0.74-3.04)	23	1.76 (1.05-2.95)	23	1.93 (1.08-3.45)
P _{trend}		0.121		0.149		0.036		0.037
Rectum								
Nonexposed	43	1.00 (reference)			43	1.00 (reference)		
T1	8	0.52 (0.24-1.14)	8	1.00 (reference)	9	0.57 (0.27-1.22)	9	1.00 (reference)
T2	13	0.75 (0.37-1.50)	13	1.39 (0.56-3.61)	8	0.55 (0.24-1.23)	8	0.94 (0.36-2.46)
T3 _L	9	1.07 (0.48-2.36)	9	1.97 (0.75-5.19)	10	1.32 (0.62-2.84)	10	0.80 (0.89-5.35)
T3 _U	4	0.66 (0.22-1.99)	4	1.17 (0.33-4.12)	7	0.85 (0.36-2.03)	7	1.43 (0.52-3.92)
P _{trend}		0.944		0.566		0.637		0.317
Bladder								
Nonexposed	48	1.00 (reference)			48	1.00 (reference)		
T1	7	0.48 (0.21-1.08)	7	1.00 (reference)	11	0.70 (0.35-1.40)	11	1.00 (reference)
T2	17	0.96 (0.51-1.84)	17	1.99 (0.80-4.93)	14	0.98 (0.50-1.89)	14	1.40 (0.63-3.12)
T3 _L	8	1.03 (0.45-2.31)	8	2.10 (0.75-5.90)	5	0.69 (0.36-1.83)	5	1.00 (0.34-2.91)
T3 _U	6	1.86 (0.41-2.71)	6	2.09 (0.65-6.69)	7	0.86 (0.36-2.05)	7	1.21 (0.46-3.22)
P _{trend}		0.543		0.34		0.84		0.922
Kidney								
Nonexposed	34	1.00 (reference)			34	1.00 (reference)		
T1	14	1.41 (0.73-2.73)	14	1.00 (reference)	12	1.21 (0.60-2.43)	12	1.00 (reference)
T2	7	0.66 (0.27-1.59)	7	0.47 (0.19-1.19)	7	0.81 (0.34-1.94)	7	0.68 (0.26-1.73)
T3 _L	3	0.66 (0.19-2.28)	3	0.49 (0.14-1.72)	2	0.49 (0.11-2.13)	2	0.42 (0.09-1.87)
T3 _U	5	2.06 (0.75-5.65)	5	1.52 (0.54-4.30)	7	1.77 (0.73-4.30)	7	1.51 (0.59-3.89)
P _{trend}		0.419		0.409		0.273		0.253

^I adjusted for age at enrollment (<40, 40-49, 50-59, >60), education (<=high school graduate or beyond high school), cigarette smoking (ever/never), alcohol consumption in the past year (ever/never), family history of cancer in first-degree relatives (yes/no), state of residence (Iowa/North Carolina), and the top five pesticides most highly correlated with trifluralin exposure (dicamba, metolachlor, imazethapyr, metribuzin, cyanazine).