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ScienceDirect
Environmental Research 107 (2008) 271–276
Environmental Research
www.elsevier.com/locate/envres

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

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Received 29 June 2007; received in revised form 28 November 2007; accepted 15 January 2008
Available online 14 March 2008

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.
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Keywords: Agriculture; Trifluralin; Pesticides; Cancer; Occupational exposure

1. 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 (EPA, 1996). Of the 24,000 tons produced worldwide in 1998, about 64% was used on soybeans, and 19% was used on cotton (http://www.pan-uk.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) (Waite et al., 2004). It was also the most frequently detected pesticide on the hands (60%) for 14 pesticides measured among 20 non-occupationally exposed adults in France (Bouvier et al., 2006).

There are a number of reports evaluating trifluralin for genotoxicity, immunotoxicity, and reproductive toxicity; although the results are not entirely consistent, trifluralin does not appear to be strongly genotoxic (Garriott et al., 1991).

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0013-9351/$ - see front matter Published by Elsevier Inc.
doi:10.1016/j.envres.2008.01.010

Genotoxic effects have been reported by experimental studies using *Drosophilia matanogaster* (Kaya et al., 2004), mouse bone-marrow cells (Gebel et al., 1997), and human peripheral lymphocytes (Ribas et al., 1995). It also influenced serum concentrations of reproductive and metabolic hormones, particularly thyroxine (Rawlings et al., 1998). However, no significant increase in the number of micronuclei was observed for cultured human peripheral lymphocytes (Ribas et al., 1996). Neither was the immune function of rat affected by trifluralin (Blakley et al., 1998).

Trifluralin is considered a possible human carcinogen by EPA based on the induction of urinary tract tumors and thyroid tumors in rats (EPA, 1996; NTP, 1978). Few epidemiologic studies of trifluralin have been conducted. A significant excess risk (OR = 12.5, 95% CI = 1.6–116.1) 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 two of 948 controls had reported to use trifluralin) (Hoar et al., 1986), but a recent pooled analysis (870 NHL cases and 2569 controls) found no association (OR = 0.9, 95% CI = 0.5–1.6) (De Roos et al., 2003).

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

2. Methods

2.1. Cohort enrollment and follow-up

The 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 (Alavanja, 1996). 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 through state cancer registries from enrollment in 1993 through 2002 and coded using the International Classification of Diseases for Oncology, Second Edition (Percy et al., 1990). 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.

2.2. 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 (Alavanja, 1999). 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 four 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 four levels: 0–162.1, 162.2–593, 593.1–1176.0, >1176.0). The highest tertile was further divided into two groups to better evaluate the effect of extreme exposure. 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 (Dosemeci, 2002).

2.3. Data analysis

Prevalent cancer cases ($n = 1075$) identified prior to the time of enrollment, and cases who did not provide information on trifluralin use

Table 1
Selected characteristics of applicators, by trifluralin exposure in the Agricultural Health Study between 1993 and 1997 ($n = 50,127$)

Characteristics	Non-exposed ($n = 24,415$) No. (%)	Low-exposed ($n = 8509$) No. (%)	High-exposed ($n = 17,203$) No. (%)
Age[a]			
<40	8699 (35.6)	2945 (34.6)	5222 (30.4)
<40–49	8699 (35.6)	2945 (34.6)	5222 (30.4)
40–49	6398 (26.2)	2340 (27.5)	5557 (32.3)
50–59	4684 (19.2)	1742 (20.5)	3710 (21.6)
> = 60	4633 (19.0)	1482 (17.4)	2713 (15.8)
Sex			
Male	23,366 (95.7)	8381 (98.5)	17,087 (99.3)
Female	1049 (4.3)	128 (1.5)	116 (0.7)
State of residence			
Iowa	13,295 (54.4)	6395 (75.2)	14,543 (84.5)
North Carolina	11,120 (45.6)	2114 (24.8)	2660 (15.5)
Applicator type			
Private	21,949 (89.9)	8089 (95.1)	15,491 (90.5)
Commercial	2466 (10.1)	420 (4.9)	1712 (9.5)
Education[a]			
High school graduate	14,651 (60.2)	4512 (53.2)	9193 (53.5)
Beyond high school	9692 (39.8)	3975 (46.8)	7989 (46.5)
Smoking[a]			
Never	12,677 (52.5)	4754 (56.1)	9309 (54.3)
Former	7124 (29.5)	2459 (29.0)	5147 (30.0)
Current	4351 (18.0)	1264 (14.9)	2695 (15.7)
Alcohol use[a]			
No	8679 (36.4)	2402 (28.7)	4167 (24.6)
Yes	15,139 (63.6)	5969 (71.3)	12,761 (75.4)
Family history of cancer[a]			
No	14,162 (62.7)	4673 (58.3)	9264 (57.0)
Yes	8627 (37.3)	3338 (41.7)	6999 (43.0)
Use of other pesticides highly correlated with trifluralin			
Dicamba	7570 (32.0)	4711 (57.4)	11,973 (71.8)
Metolachlor	6253 (26.1)	4695 (56.8)	11,544 (69.1)
Imazethayr	5057 (21.3)	4320 (52.8)	11,299 (67.9)
Metribuzin	1570 (15.2)	1729 (46.0)	5044 (65.4)
Cyanazine	6701 (23.8)	4090 (49.7)	10,236 (61.3)

[a]Numbers do not always sum to total because of missing data.