Published in final edited form as:
*Cancer Causes Control*. 2010 June ; 21(6): 871–877. doi:10.1007/s10552-010-9514-9.

# Occupational Exposure to Terbufos and the Incidence of Cancer in the Agricultural Health Study

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## Abstract

**Objective—**Terbufos is the fourth most commonly used organophosphate insecticide (OP) in the United States. Terbufos has not been demonstrated to be carcinogenic in rodents, although non-arsenical insecticides, including OPs, have been associated with excess cancer in epidemiologic studies. We investigated associations between use of terbufos and incidence of cancer.

**Methods—**The Agricultural Health Study is a prospective cohort study of 57,310 licensed pesticide applicators from Iowa and North Carolina. Detailed information about 50 pesticides, including terbufos, and potential confounders was obtained from self-administered questionnaires. Terbufos intensity-weighted lifetime exposure-days [(lifetime exposure-days) X (exposure intensity score)]. Cases include all first primary cancers diagnosed between enrollment and December 31, 2005. Hazard ratios (HR) and 95% CI were calculated with Cox proportional hazards models, adjusting for potential confounders.

**Results—**Overall cancer risk was slightly increased among terbufos users (HR 1.21 (1.06-1.37). Suggestive associations were observed between terbufos use and cancers of the prostate ($HR_{highest\ tertile}$ = 1.21; 95% CI = 0.99-1.47) and lung ($HR_{middle\ tertile}$ = 1.45; 95% CI = 0.95-2.22) and leukemia ($HR_{middle\ tertile}$ = 2.38; 95% CI = 1.35-4.21) and non-Hodgkin lymphoma ($HR_{middle\ tertile}$ = 1.94; 95% CI = 1.16-3.22), although the exposure-response gradients were non-monotonic and *p* for trends were not significant.

**Conclusion—**We found suggestive associations between occupational terbufos use and several cancer sites. However, cautious interpretation of these results is warranted by the lack of existing experimental and epidemiologic evidence to support carcinogenic effects of terbufos.

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## Introduction

Terbufos (*S-tert*-butylthiomethyl *O,O*-diethyl phosphorodithioate), a systemic insecticide, is the fourth most commonly used organophosphate insecticide (OP) in the United States, with an estimated 3 to 5 million pounds applied in 2001 (1). First registered for use in the United States in 1974, terbufos was initially used to control insects and nematodes on corn. Currently, terbufos is also registered for use on sugar beets, sorghum, and bananas; terbufos is not registered for residential use or in public health applications (2).

Terbufos is metabolized and activated to its neurotoxic form via oxidative desulfuration. This active form of terbufos irreversibly inhibits acetylcholinesterase, leading to the accumulation of acetylcholine and the classic signs and symptoms associated with muscarinic and nicotinic receptor overstimulation (3). The United States Environmental Protection Agency (USEPA) classifies terbufos in toxicity category I (high acute toxicity), but as group E for carcinogenicity (evidence of non-carcinogenicity for humans). This group E carcinogenicity classification is based largely on the lack of carcinogenic effects in two animal studies and lack of mutagenicity in several short-term genotoxicity assays (4). One published study reported mixed results with terbufos testing positive for genotoxicity in *Saccharomyces*, but not in *Salmonella* assays (5).

The International Agency for Research on Cancer (IARC) classifies occupational spraying and application of non-arsenical insecticides, including OPs, as probably carcinogenic to humans (6), although terbufos has not been specifically evaluated by IARC. In previous epidemiologic reports from the Agricultural Health Study (AHS) of specific cancer sites, terbufos use was not associated with cancers of the prostate (7), lung (8), breast (9), colon and rectum (10) or pancreas (11); other cancer sites have not been examined. However, several OPs, including chlorpyrifos (12), diazinon (13), and fonofos (14), have been associated with select cancers in the AHS. Despite the lack of clear evidence for carcinogenicity, several biologic mechanisms have been postulated for organophosphate insecticides, in general, including mitogenic effects (15), oxidative stress (16), and immunotoxicity (17). Although the epidemiologic and experimental evidence for the carcinogenicity of terbufos are limited, the widespread use of terbufos, and possible associations with insecticides and other OPs prompted the current investigation of terbufos in the AHS.

## Materials and Methods

The AHS is a prospective cohort study of 57,310 licensed pesticide applicators and 32,347 spouses of these applicators from Iowa and North Carolina (18). Licensed pesticide applicators include farmers (private applicators) and commercial applicators employed by pest control companies or businesses such as warehouses and grain elevators that regularly use pesticides on their premises. Recruitment began December 13, 1993 and ended December 31, 1997. The vital status of the cohort members is determined via annual linkages with the National Death Index and state death registries. Incident cancers were identified through state tumor registries and coded according to the International Classification of Diseases for Oncology (ICD-O-2) (19). Cancer cases consist of incident, first primary cancers diagnosed between enrollment in the cohort and December 31, 2005 (AHS Data Release P1REL0612). The average follow-up time was 10.6 (SD = 2.1) years. The current analysis does not include spouses of licensed pesticide applicators. Among these 57,310 applicators, prevalent cancer cases ($n$ = 1,083), those missing information about terbufos use ($n$ =6,094), and potential confounders ($n$ = 5,509) were excluded, leaving 44,624 cohort members for this analysis. Participants ($n$=945) who moved out of Iowa or North Carolina were censored at the year they moved. The protocol was approved by all appropriate Institutional Review Boards and all participants provided informed consent.

## Exposure assessment

At enrollment, participants completed a self-administered questionnaire (http://www.aghealth.org/questionnaires.html) and reported the lifetime use (ever/never) of 50 pesticides. For 22 of these pesticides, including terbufos, applicators also reported the number of years and days per year they personally mixed or applied each of these pesticides. The enrollment questionnaire also gathered information on application methods and the use of personal protective equipment (PPE), smoking history, alcohol consumption, fruit and vegetable consumption, other agricultural activities, and non-farm occupational exposures.

Lifetime exposure-days to terbufos were initially calculated as the product of the number of years a participant personally mixed or applied terbufos and the number of days in an average year they used terbufos. In addition, an exposure intensity score was estimated based on an algorithm developed by Dosemeci et al. (20) and used to calculate intensity-weighted lifetime exposure-days to terbufos [exposure intensity score × lifetime exposure-days]. This exposure intensity score weights specific activities related to pesticide use that may modify the intensity of exposure. The algorithm includes whether an applicator personally mixed or loaded pesticides for application, application methods used, repair of pesticide application equipment, and PPE use during pesticide handling activities. Dermal absorption is considered the major route of exposure for pesticide applicators (21). Consequently, the exposure intensity score heavily weighted the use of protective gloves and to a lesser extent on other protective clothing.

## Statistical analysis

Hazard ratios (HR) and 95 percent confidence intervals (CI) were calculated with Cox Proportional Hazards models using SAS 9.1 software (22). Attained age was used as the survival time metric. Ten cancer sites had sufficient numbers of cases for statistical analyses (i.e., $\geq 5$ cases per category of exposure), including lymphatic-hematopoietic cancers combined (i.e., multiple myeloma, leukemia, Hodgkin's lymphoma and non-Hodgkin lymphoma (NHL)), leukemia, NHL, melanoma, and cancers of the lung, prostate, colon, oral cavity, kidney, and bladder. Categories for intensity-weighted lifetime exposure-days to terbufos were determined by tertiles of the exposure distribution among all of the exposed cancer cases combined to ensure sufficient number of cases per exposure category.

Models were adjusted for factors frequently hypothesized to be potential confounders in epidemiologic studies of pesticide exposure and cancer, including sex, education ($\leq$ high school graduate, > high school graduate), cigarette smoking status (never, former, or current), alcohol consumption during the last 12 months (yes or no), history of cancer in a 1$^{st}$ degree relative (yes or no), year at enrollment, and state of residence (Iowa or North Carolina).

The use of multiple pesticides by applicators has been postulated as a source of important potential confounding in epidemiologic studies of pesticide exposure and cancer (23). Consequently, the five pesticides most highly correlated with terbufos use were also included in our models. We identified the five most correlated pesticides by calculating Spearman correlation coefficients between terbufos and these other pesticides (carbofuran (r = 0.56); fonofos (r = 0.56); atrazine (r = 0.44); 2,4-D (r = 0.38), and phorate (r =0.31)). None of the other pesticides were negatively correlated with terbufos.

We conducted analyses utilizing two reference groups: (1) pesticide applicators who reported never using terbufos and (2) pesticide applicators whose use of terbufos was in the lowest tertile of exposure. The low-exposed group was used because of a concern that applicators who reported using terbufos may differ systematically from those who did not report using terbufos with regard to unmeasured cancer risk factors. Use of the low-exposed referent group may mitigate the potential for such differences to confound associations.

Analyses were also stratified by state of residence (Iowa and North Carolina) and applicator type (private and commercial) to assess the internal consistency of the risk estimates. Linear trends were assessed using the *p*-value of the coefficient of the exposure treated as a continuous variable using the median value for each tertile of exposure in the models while adjusting for aforementioned covariates (24).

## Results

Thirty-seven percent (16,489/44,624) of the licensed applicators reported ever using terbufos. Applicators, who reported using terbufos also reported applying a greater average number of other pesticides, were more likely to grow corn, reside in Iowa, drink alcohol in the last 12 months, and have a family history of cancer compared with applicators who reported never using terbufos (Table 1). Notably, the mean number of pesticides used increased across tertiles of terbufos intensity-weighted lifetime exposure-days. Distributions for smoking (pack-years), age, and education were not meaningfully different between those who used and those who did not use terbufos.

Intensity-weighted lifetime exposure-days of terbufos were positively associated with the risk of all cancers combined, regardless of the referent group (Table 2). However, the exposure-response gradients were not monotonic and the test for linear trend was statistically significant ($p$ trend = 0.004) only when the non-exposed were used as the referent group.

Monotonic exposure response gradients among specific cancer sites and terbufos use were not readily apparent (Table 2). However, the risk estimates for terbufos use and several cancer sites were suggestive of potential associations. These sites include lymphatic-hematopoietic cancers and cancers of the prostate and lung. Cancers of the colon, bladder, oral cavity, kidney and melanoma were not associated with intensity-weighted lifetime exposure-day of terbufos.

The hazard ratios, regardless of the exposure category, for prostate cancer were slightly increased compared with non-users, although the exposure-response gradient was not monotonic ($p$ trend = 0.12). No such increase in the HRs were observed when the low-exposed were used as the referent, although this would be expected given the initial jump in the incidence of prostate cancer observed among the low-exposed when the non-exposed were used as the referent group. For lung cancer, the HRs were slightly increased in the two highest exposure categories regardless of the referent group, although neither the exposure-response gradients were monotonic nor the $p$ for trends statistically significant.

For the lymphatic-hematopoietic cancers combined, the HRs were increased in the two highest exposure categories, regardless of the referent group. The greatest HR was observed in the middle exposure category (>107-352 intensity-weighted lifetime exposure days). Similar patterns in risk were observed for leukemia and NHL, although the associations were substantially larger for leukemia than either NHL or all lymphatic-hematopoietic cancers combined. The tests for linear trend were not significant for any of these sites, regardless of the referent group.

We conducted additional sub-group analyses stratified by state of residence (i.e., Iowa and North Carolina) and found that the risk estimates were similar for all cancers combined and prostate cancer between pesticide applicators residing in Iowa and North Carolina (data not shown). For the other cancer sites, there were too few cases in North Carolina for meaningful analysis. Likewise, the number of commercial applicators was also insufficient for analyses stratified by applicator type (i.e., private and commercial). Notwithstanding, the results for the private applicators alone were largely unchanged (data not shown).

## Discussion

Although a weak statistical association was observed with all cancers combined, associations with specific cancers were only suggestive. It is possible that our current analyses were underpowered for specific cancer sites and as a consequence, we were unable to detect which, if any, sites were associated with terbufos use.

Increases in site-specific cancer risk have not been found in the previous epidemiologic studies that have assessed occupational exposure to terbufos and cancer risk. For instance, terbufos was not associated with the risk for cancer of the prostate or lung in two previous reports from the AHS (7-8) and Cantor et al. (25) found no association between ever handling terbufos and NHL in a case-control study among men in Iowa and Minnesota (OR = 0.9; 95%CI = 0.5-1.7). Moreover, a pooled analysis of three case-control studies (26) found no association between terbufos and NHL (OR = 0.8; 95%CI = 0.4-1.8). However, a non-significant increase in leukemia was found in a case-control study of men in Iowa and Minnesota (OR = 1.3; 95% CI = 0.7-2.4) (27). We also found a suggestive association between terbufos and leukemia. The middle tertile of terbufos use was associated with higher incidence of leukemia compared with either referent group (non-exposed or low exposed), although there was little evidence of an exposure-response gradient.

Several issues should be considered in evaluating our results. With the exception of prostate cancer, there were relatively small numbers of cancer cases in the three exposure categories and consequently limited study power may have made it difficult to detect an association if one exists. However, the number of terbufos exposed NHL ($n$ = 47) and leukemia ($n$ = 37) cases in our study was substantially greater than the number of terbufos exposed in the previous case-control studies of NHL ($n$ = 15) and leukemia ($n$ = 16) conducted in men from Iowa and Minnesota (25-27).

Lack of information on other specific agricultural exposures is often a concern in epidemiologic studies of pesticide exposure (28). In this study, however, we were able to consider exposure to 49 other pesticides and other known risk factors for cancer which permit statistical control for these potential confounders in our analyses.

Exposure misclassification is another potential limitation. The use of self-administered questionnaires to ascertain lifetime use of pesticides undoubtedly introduces some exposure misclassification, which would tend to bias relative risks toward the null in a prospective study such as the AHS (29). Nonetheless, Blair et al. (30) have demonstrated that farmers in the Agricultural Health Study have good reliability for reporting terbufos use (% exact agreement = 83), indicating that the reliability of the pesticide use questions in the AHS is similar to other factors routinely obtained by questionnaire for epidemiologic studies. Hoppin et al. (31) has also examined accuracy of the self-report of duration and decade of first use and found that only 1% of terbufos users over-reported the duration of use and that 3% over-estimated the decade of first use. Furthermore, Thomas et al. (32) has assessed the accuracy of the intensity score, used in the intensity-weighted lifetime exposure-days metric, among a sub-study of the AHS cohort that found a moderate correlation between the intensity score and the urinary concentration of 3,5,6-trichloro-2-pyridinol, the major metabolite of chlorpyrifos, an organophosphate insecticide (Spearman's correlation coefficient = 0.53; $p$-value = 0.035). These indirect assessments of the validity of the AHS exposure assessment suggest that exposure misclassification may not be extensive; however it may still have contributed towards obscuring the suggestive associations for cancer of the prostate and lung and the lymphatic-hematopoietic cancers

In summary, there was some suggestion that cancers of the prostate and lung as well as leukemia and non-Hodgkin lymphoma may be associated with terbufos use. However, this interpretation

is complicated by the lack of experimental evidence that terbufos is a carcinogen, previous epidemiologic evidence for such associations, and the lack exposure-response gradients in our data.

## Acknowledgments

This work was supported [in part] by the intramural research program of the National Institutes of Health, the National Institute of Environmental Health Sciences (Z01-ES049030-11) and National Cancer Institute (Z01-CP010119).

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**Table 1**

Baseline Characteristics by intensity-weighted lifetime exposure-days to terbufos, Agricultural Health Study (1993-1997)

| Characteristic | Terbufos Intensity-Weighted Lifetime Exposure-Days (n=44,624) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Non-exposed (n=28,135) | | Tertile 1 >0-107 (n=5,722) | | Tertile 2 >107-352 (n=5,204) | | Tertile 3 >352 (n=5,563) | |
| | Number | % | Number | % | Number | % | Number | % |
| Age (years) | | | | | | | | |
| < 40 | 10,818 | 38.45 | 2,076 | 36.28 | 1,784 | 34.28 | 1,951 | 35.07 |
| 40 – 49 | 7,650 | 27.19 | 1,779 | 31.09 | 1,623 | 31.19 | 1,771 | 31.84 |
| 50 – 59 | 5,380 | 19.12 | 1,110 | 19.40 | 1,098 | 21.10 | 1,147 | 20.62 |
| ≥ 60 | 4,287 | 15.24 | 757 | 13.23 | 699 | 13.43 | 694 | 12.48 |
| Sex | | | | | | | | |
| Male | 27,140 | 96.49 | 5,676 | 96.46 | 5,173 | 99.40 | 5,533 | 99.46 |
| Female | 995 | 3.54 | 995 | 0.80 | 31 | 0.60 | 30 | 0.54 |
| Ethnicity | | | | | | | | |
| White | 27,483 | 97.79 | 5,665 | 99.11 | 5,166 | 99.35 | 5,511 | 99.21 |
| Black | 484 | 1.72 | 31 | 0.54 | 25 | 0.48 | 34 | 0.61 |
| Other | 138 | 0.49 | 20 | 0.35 | 9 | 0.17 | 10 | 0.18 |
| State | | | | | | | | |
| North Carolina | 9,995 | 35.53 | 766 | 13.39 | 888 | 17.06 | 1,364 | 24.52 |
| Iowa | 18,140 | 64.47 | 4,956 | 86.61 | 4,316 | 82.94 | 4,199 | 75.48 |
| Applicator type | | | | | | | | |
| Commercial | 3,531 | 12.55 | 272 | 4.75 | 191 | 3.67 | 289 | 5.20 |
| Farmer | 24,604 | 87.45 | 5,450 | 95.25 | 5,013 | 96.33 | 5,274 | 94.80 |
| Smoking | | | | | | | | |
| Never | 14,921 | 53.03 | 3,392 | 59.28 | 3,034 | 58.30 | 3,091 | 55.56 |
| Former | 8,169 | 29.04 | 1,601 | 27.98 | 1,477 | 28.38 | 1,588 | 28.55 |
| Current | 5,045 | 17.93 | 729 | 12.74 | 693 | 13.32 | 884 | 15.89 |
| Alcohol use in last 12 months | | | | | | | | |
| Yes | 18,936 | 67.30 | 4,290 | 74.97 | 3,924 | 75.40 | 4,204 | 75.57 |
| Education | | | | | | | | |
| ≤ High school | 15,456 | 54.94 | 2,975 | 51.99 | 2,751 | 52.86 | 3,061 | 55.02 |
| > High school | 12,679 | 45.06 | 2,747 | 48.01 | 2,453 | 47.14 | 2,502 | 44.98 |

| Characteristic | Terbufos Intensity-Weighted Lifetime Exposure-Days (n=44,624) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Non-exposed (n=28,135) | | Tertile 1 >0-107 (n=5,722) | | Tertile 2 >107-352 (n=5,204) | | Tertile 3 >352 (n=5,563) | |
| Family history of cancer | | | | | | | | |
| Yes | 11,055 | 39.29 | 2,489 | 43.50 | 2,256 | 43.35 | 2,434 | 43.75 |
| Corn production | | | | | | | | |
| Yes | 18,417 | 65.46 | 5,207 | 91.00 | 4,797 | 92.18 | 5,055 | 90.87 |
| | Mean (SD) | | | | | | | |
| Smoking (pack-years) | | | | | | | | |
| Former smokers | 15.54 (19.92) | | 12.97 (16.80) | | 13.61 (17.71) | | 14.65 (19.43) | |
| Current smokers | 22.57 (20.15) | | 22.64 (21.11) | | 22.44 (18.85) | | 23.04 (19.55) | |
| Number of other pesticides used | 11.38 (6.83) | | 15.61 (6.95) | | 16.56 (7.35) | | 17.99 (7.35) | |
| Follow-up (years) | 10.61 (2.09) | | 10.54 (2.00) | | 10.50 (2.07) | | 10.54 (2.05) | |

Categorical variables presented as n, %; continuous variables presented as mean ± SD.



*Cancer Causes Control*. Author manuscript; available in PMC 2010 September 8.

**Table 2**

Hazard ratios for selected cancers, by intensity-weighted lifetime exposure-days to terbufos among Agricultural Health Study pesticide applicators (1993-1997)

| | | Non-exposed Referent | | Low Exposed Referent | |
|---|---|---|---|---|---|
| | Cases (*n*) | HR*,† | 95% CI* | HR | 95% CI |
| Intensity-weighted Life-time Exposure days‡ | | | | | |
| **All Cancers** | | | | | |
| 0 | 1,777 | 1.0 | Ref.* | | |
| >0-107 | 319 | 1.05 | (0.92-1.19) | 1.0 | Ref. |
| >107-352 | 360 | 1.26 | (1.12-1.43) | 1.22 | (1.05-1.42) |
| >352 | 346 | 1.21 | (1.06-1.37) | 1.18 | (1.01-1.37) |
| Trend§ | | | 0.004 | | 0.19 |
| **Prostate Cancer** | | | | | |
| 0 | 684 | 1.0 | Ref. | | |
| >0-107 | 151 | 1.19 | (0.99-1.44) | 1.0 | Ref. |
| >107-352 | 152 | 1.28 | (1.06-1.55) | 1.09 | (0.87-1.37) |
| >352 | 144 | 1.21 | (0.99-1.47) | 1.02 | (0.81-1.29) |
| Trend§ | | | 0.12 | | 0.93 |
| **Lung Cancer** | | | | | |
| 0 | 180 | 1.0 | Ref. | | |
| >0-107 | 17 | 0.79 | (0.47-1.33) | 1.0 | Ref. |
| >107-352 | 30 | 1.45 | (0.95-2.22) | 1.83 | (1.00-3.33) |
| >352 | 24 | 1.13 | (0.71-1.79) | 1.36 | (0.72-2.56) |
| Trend§ | | | 0.47 | | 0.85 |
| **Colon Cancer** | | | | | |
| 0 | 135 | 1.0 | Ref. | | |
| >0-107 | 21 | 0.94 | (0.52-1.36) | 1.0 | Ref. |
| >107-352 | 15 | 0.63 | (0.36-1.11) | 0.77 | (0.40-1.50) |
| >352 | 32 | 1.39 | (0.91-2.13) | 1.77 | (1.01-3.10) |
| Trend§ | | | 0.08 | | 0.009 |
| **Bladder Cancer** | | | | | |

| | | Non-exposed Referent | | Low Exposed Referent | |
|---|---|---|---|---|---|
| | Cases (*n*) | HR*,† | 95% CI* | HR | 95% CI |
| 0 | 88 | 1.0 | Ref. | | |
| >0-107 | 12 | 0.86 | (0.46-1.63) | 1.0 | Ref. |
| >107-352 | 12 | 0.94 | (0.49-1.78) | 1.19 | (0.53-2.67) |
| >352 | 12 | 0.95 | (0.50-1.83) | 1.20 | (0.52-2.74) |
| Trend§ | | 0.94 | | 0.74 | |
| **Lymphatic-hematopoietic Cancers** | | | | | |
| 0 | 167 | 1.0 | Ref. | | |
| >0-107 | 31 | 1.05 | (0.70-1.58) | 1.0 | Ref. |
| >107-352 | 50 | 1.85 | (1.31-2.62) | 1.75 | (1.12-2.75) |
| >352 | 33 | 1.25 | (0.83-1.87) | 1.21 | (0.74-1.99) |
| Trend§ | | 0.27 | | 0.92 | |
| **Leukemia** | | | | | |
| 0 | 58 | 1.0 | Ref | | |
| >0-107 | 7 | 0.75 | (0.33-1.69) | 1.0 | Ref. |
| >107-352 | 20 | 2.38 | (1.35-4.21) | 3.13 | (1.32-7.43) |
| >352 | 11 | 1.37 | (0.69-2.75) | 1.82 | (0.7-4.74) |
| Trend§ | | 0.28 | | 0.83 | |
| **Non-Hodgkin Lymphoma** | | | | | |
| 0 | 69 | 1.0 | Ref. | | |
| >0-107 | 17 | 1.28 | (0.73-2.26) | 1.0 | Ref. |
| >107-352 | 24 | 1.94 | (1.16-3.22) | 1.50 | (0.80-2.79) |
| >352 | 15 | 1.22 | (0.67-2.22) | 0.96 | (0.48-1.94) |
| Trend§ | | 0.62 | | 0.55 | |
| **Oral Cavity Cancer** | | | | | |
| 0 | 45 | 1.0 | Ref. | | |
| >0-107 | 9 | 1.22 | (0.57-2.61) | 1.0 | Ref. |
| >107-352 | 7 | 1.04 | (0.45-2.41) | 0.88 | (0.33-2.36) |
| >352 | 10 | 1.45 | (0.69-3.05) | 1.26 | (0.50-3.15) |
| Trend§ | | 0.37 | | 0.51 | |
| **Kidney Cancer** | | | | | |

| | | Non-exposed Referent | | Low Exposed Referent | |
|---|---|---|---|---|---|
| | Cases (*n*) | HR*,† | 95% CI* | HR | 95% CI |
| 0 | 47 | 1.0 | Ref. | | |
| >0-107 | 11 | 1.31 | (0.66-2.63) | 1.0 | Ref. |
| >107-352 | 12 | 1.59 | (0.810-3.15) | 1.18 | (0.52-2.69) |
| >352 | 5 | 0.68 | (0.26-1.78) | 0.48 | (0.17-1.40) |
| Trend§ | | 0.42 | | 0.12 | |
| | | **Melanoma** | | | |
| 0 | 77 | 1.0 | Ref. | | |
| >0-107 | 14 | 1.00 | (0.55-1.83) | 1.0 | Ref. |
| >107-352 | 17 | 1.29 | (0.73-2.28) | 1.25 | (0.61-2.54) |
| >352 | 12 | 0.88 | (0.46-1.68) | 0.86 | (0.39-1.87) |
| Trend§ | | 0.71 | | 0.50 | |

*RR, CI, confidence interval; Ref., reference group

†Hazard ratio adjusted for age, gender, education, family history of cancer, smoking, alcohol, year of enrollment, state of residence, atrazine, 2,4-D, fonofos, carbofuran, and phorate

‡Intensity-weighted Lifetime exposure days = years of use × day of use per year × intensity score

§*p*-value for trend test.