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Cancer incidence among pesticide applicators exposed to butylate in the agricultural health study (AHS)

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Abstract

Although limited, epidemiologic studies suggest possible associations between butylate use and cancer risk, specifically prostate cancer and non-Hodgkin lymphoma (NHL). We examined butylate use and cancer risk more broadly in the AHS, a cohort of licensed pesticide applicators in Iowa and North Carolina. Pesticide use information was collected using self-administered questionnaires. Poisson regression was used to calculate rate ratios (RR) and 95% confidence intervals (CI). Two exposure metrics were used: lifetime exposure days (LD) and intensity-weighted lifetime exposure days (IWLD). We used two referent groups: unexposed to butylate and the lowest butylate usage category. This analysis included 19,655 applicators with complete butylate use information; 5,297 applicators were exposed to butylate, making this the largest study of butylate to-date. The mean follow-up time since enrollment was 9 years. Prostate cancer risk was significantly elevated among applicators in the highest LD category in both referent groups (low exposed referent: $RR_{LD}=2.09$, 95% CI=1.27–3.44). We observed a significantly elevated joint effect of prostate cancer family history and high butylate usage across both exposure metrics and both referent groups (low exposed referent: $RR_{LD}=2.00$, 95% CI=1.07–3.74), and a non-significant, elevated interaction between butylate use and prostate cancer family history, similar to a previous AHS finding. Statistically significant increased risks and exposure-response trends were seen for all lymphohematopoietic cancers (AL) and NHL for both exposure metrics and referent groups (low exposed referent: AL: $RR_{LD}=2.27$, 95% CI = 1.18–4.37; NHL: $RR_{LD}=3.44$, 95% CI = 1.29–9.21). Our analysis did not find meaningful associations for other cancers analyzed. Further study is warranted for AL, NHL and prostate cancers.

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Keywords

butylate; pesticide; cancer; agricultural health study

Introduction

Butylate, a thiocarbamate herbicide, is used on corn and grassy and broadleaf weeds and nutsedge. Because butylate is highly volatile, applications are immediately incorporated into the soil to maximize effect on weeds [United States Environmental Protection Agency (USEPA), 1993a]. Butylate formulations include emulsifiable concentrates, a granular form, and an encapsulated form (USEPA, 1993b). Given butylate's high volatility, humans are exposed mainly through dermal and respiratory exposure routes (USEPA, 2001).

Butylate was first registered as an herbicide in the United States in 1967 (USEPA, 2001) and is widely used. According to a 1993 report, between 6 and 15 million pounds of butylate are applied annually, treating 2 to 7% of the field corn grown in the United States (USEPA, 1993b). Although butylate usage and production are expected to decline with the introduction of newer herbicides in the United States (USEPA, 2001), butylate use continues in other countries (e.g. India, Hungary, and Canada) (Pesticide Action Network, 2006).

The current state of knowledge on the health effects of butylate is minimal and inconsistent. Like other thiocarbamate pesticides, neurotoxicity is considered the major toxic effect (USEPA, 1993a). Butylate tested *in situ* with the *Zea mays* pollen waxy locus assay was not genotoxic (Plewa et al., 1984). Evidence of mutagenicity was seen in mice given an oral dose of butylate (National Institute of Occupational Health and Safety (NIOSH), 1986) and in mouse lymphoma cells treated with butylate (Janess, 1986), but was not mutagenic in the Ames test performed on *Salmonella* (USEPA, 1989).

Butylate does not appear to induce malignant tumors in experimental animals, although evaluation of oncogenicity was inadequate in mice due to lack of confirmatory histopathology [USEPA, 2001; California Environmental Protection Agency (CAEPA, 1998)]. Based on these studies and the presumption that butylate is of low toxicity to worker populations (USEPA, 1993b) and the general public, the Environmental Protection Agency classified butylate as a "Group E" carcinogen (evidence of non-carcinogenicity for humans) in a report released in 2001 (USEPA, 2001).

The epidemiologic evidence linking butylate with cancer, on the other hand, is suggestive, but inconclusive. Several epidemiologic investigations have examined exposure to carbamate pesticides, including butylate, and the risk of cancer. McDuffie et al. (2001), found a nonstatistically significant elevated risk for non-Hodgkin lymphoma (NHL) associated with the use of thiocarbamate pesticides (odds ratio [OR] = 1.41; 95% confidence interval [CI], 0.62– 2.20). Zheng et al. (2001) also observed an elevated risk of NHL among farmers who ever used carbamate herbicides in general (OR = 1.5; 95% CI, 1.1–2.3) and butylate specifically (OR = 1.6; 95% CI, 1.0–2.4), though only 45 cases and 76 controls were exposed to butylate, and most farmers had not personally applied it. Recent data from the Agricultural Health Study (AHS) found an increased risk of prostate cancer among study participants exposed to butylate with a family history of prostate cancer, but not among those subjects without a family history (Alavanja et al., 2003). Given the limited carcinogenic and epidemiologic information available on cancer in butylate-exposed populations, we examined the association between butylate use and any cancer with 10 or more exposed cases in the AHS, thus conducting the largest study of butylate to-date.

Methods

Cohort enrollment and follow-up

The AHS is a prospective study of 57,310 licensed pesticide applicators and their spouses who live in Iowa and North Carolina (Alavanja et al., 1996) and were recruited between December 1993 and December 1997 from mandatory certification sessions for using EPA-designated Restricted Use Pesticides (Alavanja et al., 1999). Members of the AHS cohort were matched to cancer registry files in both states for case identification and to state death registries and the National Death Index to ascertain vital status. Incident cancers were identified for the time period from the date of enrollment through December 2004 and were coded according to the *International Classification of Diseases for Oncology, 2nd edition (ICD-O-2)*. Residence information was verified through current address records of the Internal Revenue Service (address information only), motor vehicle registration offices, and pesticide license registries of the state agricultural departments. Observations were censored in the year of death or movement out of either state. The mean length of follow-up as of December 2004 was 9.14 years. All participants provided informed consent, and the protocol was approved by all appropriate institutional review boards (IRBs).

Exposure assessment

Study participants were asked to complete a self-administered questionnaire at the time of enrollment, which collected comprehensive exposure data on 22 pesticides, information on ever/never use for 28 additional pesticides, and use of personal protective equipment, pesticide application methods, pesticide mixing, equipment repair, lifestyle factors, cancer history, and other demographic factors. For the 28 pesticides with ever/never data from the enrollment questionnaire, including butylate, more comprehensive exposure data were obtained using the take-home questionnaire; therefore, detailed information on butylate was provided on the take-home questionnaire. The questionnaires may be accessed at <http://www.aghealth.org/questionnaires.html> (National Institutes of Health, 2004).

We constructed two cumulative lifetime butylate exposure metrics: lifetime days (LD), defined as years of use $\times$ number of days used per year, and intensity-weighted lifetime exposure days (IWLD), defined as years of use $\times$ number of days used per year $\times$ intensity level. Intensity level, which incorporates factors that modify pesticide exposure, was estimated using questionnaire data from enrollment and measurement data from other published pesticide exposure literature as follows: intensity level = (mixing status + application method + equipment repair status) $\times$ personal protective equipment use (Dosemeci, 2002).

Among exposed applicators, we categorized the LD and IWLD exposure metrics into low- and high-exposure categories, based on the distribution of all cancer cases (1–25, 26 LD and 1–157, 158 IWLD, so that we could have common metrics for all cancers analyzed. Because the number of exposed cases for all cancers and prostate cancer was large, we categorized the exposure metrics into quartiles based on all cancer cases to obtain more distinct exposure-response categories (1–9, 10–25, 26–56, 57 LD, and 1–55, 56–157, 158–351, 352 IWLD).

Statistical analysis

Our analysis included 19,655 applicators who completed the take-home questionnaire. Approximately 44% of applicators with complete information who filled out the enrollment questionnaire ($n=53,927$), also completed the take-home questionnaire ($n=23,728$). After accounting for incident cases only, prevalent cancer cases diagnosed prior to enrollment were excluded ($n=1,075$), as were applicators who did not include detailed information on

butylate or were missing other confounding variables included in our statistical model ($n = 4073$), thus leaving 19,655 applicators for analysis. Because the confounder distribution may differ by use of butylate, we conducted analyses using both the non-exposed and the low-exposed groups as referents. We investigated those cancer sites for which there were 10 or more exposed incident cancer cases. Specifically, we examined cancers of the prostate, lung, colon, melanoma, bladder, leukemia, oral cavity and NHL. We also examined groupings of all cancers combined and all lymphohematopoietic cancers (consisting of NHL, Hodgkin lymphoma, leukemia, and multiple myeloma).

Statistical analyses were conducted in AHS data release version PIREL0612 using SAS version 9.1. Poisson regression was used to estimate rate ratios (RRs) and 95% confidence intervals while adjusting for the following confounding factors in all of cancer models, age at enrollment (as a continuous variable), sex, race, smoking status, education, and family history of cancer in first-degree relatives (yes/no for specific cancer site). Further adjustment for use of atrazine (sometimes used in combination with butylate (USEPA, 1993b)), and the 5 pesticides most highly correlated with butylate, that is, metribuzin, chlorimuron-ethyl, pendimethalin, aldrin, and ziram, did not affect point estimates by more than 10% between butylate use and cancers studied in this analysis; therefore, they were not included in the model. Correlated pesticides were determined based on the strength of the correlation coefficient for intensity-weighted lifetime days of exposure between butylate and the other pesticides (highest: $r = 0.60$ [metribuzin]; lowest: $r = 0.43$ [chlorimuron-ethyl, pendimethalin, aldrin, ziram]). To further investigate certain findings, we made additional adjustments for solvent use, sun exposure, and physical activity based on previously published associations for select cancers (Adami et al., 1999; Ballard-Barbash et al., 1990; Fritschi et al., 2005; Hartge et al., 2006; Kato et al., 2005; Lee et al., 1997; Mehlman, 2006; Rushton et al., 1997). Tests for trend were carried out using the midpoints of each quartile or category entered into the model as a continuous variable; all statistical tests were two-sided. Tests for trend were calculated only when more than one exposure category was analyzed.

We also stratified the risk of prostate cancer by history of prostate cancer among first-degree relatives. To test for effect modification, we created an interaction term by taking the cross product of family history of prostate cancer and the highest lifetime exposure days category, using those subjects with low exposure to butylate as the referent group.

Results

Table 1 shows the selected characteristics of the study population. Among the 19,655 subjects with complete exposure information, 5,310 who were not missing butylate exposure information or missing other variables included in our statistical model reported ever having used butylate. The cohort was comprised mostly of white, male, private applicators, which reflected the study population demographics. Applicators never exposed to butylate were similar to those in the higher exposed reference groups in terms of smoking and applicator type. However, the two exposed groups were more similar to each other than to the unexposed group in respect to most categories, notably family history of cancer, age, highest attained education, state of residence, and the five most highly correlated pesticides. Based on the observed differences between the nonexposed and either of the two exposed groups, the lowest exposed group appears to be the more appropriate referent group. However, we also present findings using the nonexposed group as the referent to further evaluate consistency of results and to utilize the additional power gained by using the nonexposed group as the referent.

The RRs for selected cancers among butylate-exposed applicators are presented in Table 2. Risk of all cancers combined was not meaningfully associated with either exposure metric

using the non-exposed group as the reference, though RRs were significantly decreased for those in the lowest butylate exposure category. We found a statistically significant exposure-response trend ($p = 0.01$) for all cancers combined for LD, resulting in a rate ratio of $RR_{LD} = 1.70$, 95% CI = 1.20–2.40 for the highest exposure quartile, using the low exposed as the referent. A slight excess was also observed using the IWLD metric, but the exposure-response trend was not statistically significant.

Prostate cancer was the most frequent cancer (153 exposed cases). Using both referent groups, butylate LD was associated with a statistically significant exposure-response trend (nonexposed $p_{trend} = 0.03$; low exposed $p_{trend} = 0.004$) and elevated RRs of 1.44 (95% CI = 1.04–2.00) and 2.09 (95% CI, 1.27–3.44) and in the highest exposure quartile using the nonexposed and low exposed referent, respectively. Excess prostate cancer risk was also observed in the highest quartile for IWLD using both referent groups, and while there was a suggestion of trend, the exposure-response trends were not statistically significant.

A statistically significant elevated risk of all lymphohematopoietic (AL) cancers and NHL was observed using both LD and IWLD and for both referent groups, with statistically significant exposure-response trends noted in the nonexposed group ((nonexposed referent [AL: $RR_{LD} = 1.84$, 95% CI = 1.14–2.97, LD $p_{trend} = 0.01$, $RR_{IWLD} = 1.98$, 95% CI = 1.26–3.10, IWLD $p_{trend} = 0.003$]; [NHL: $RR_{LD} = 2.94$, 95% CI = 1.49–5.76, $RR_{IWLD} = 2.87$, 95% CI = 1.49–5.53; LD and IWLD $p_{trend} = 0.002$]); (low exposed: [AL: $RR_{LD} = 2.27$, 95% CI = 1.18–4.37, $RR_{IWLD} = 3.02$, 95% CI = 1.52–6.03]; [NHL: $RR_{LD} = 3.44$, 95% CI = 1.29–9.21, $RR_{IWLD} = 3.69$, 95% CI = 1.31–10.38])). There were a small number of leukemia cases ($n = 11$). For leukemia, RRs were not significantly elevated and tests for trend were not significant for both exposure metrics and both referent groups. There were too few exposed cases to investigate other lymphohematopoietic cancers, including multiple myeloma ($n=7$) and Hodgkin disease ($n = 2$).

To further investigate the findings with AL and NHL, we adjusted risk estimates for ever exposure to solvents and sunlight using both referent groups. Ever exposure to solvents was defined as ever exposure to gasoline for cleaning hands/equipment outside or during the growing season and/or ever use of other solvents like paint stripper, turpentine, and benzene for cleaning outside or during the growing season, and/or non-farm occupational exposure to solvents or gasoline. Rate ratios remained elevated and statistically significant for AL cancers and NHL for both exposure metrics and both reference groups while adjusting for solvent exposure (low-exposed referent: [AL: $RR_{LD} = 4.70$, 95% CI = 1.85–11.9, $RR_{IWLD} = 2.53$, 95% CI = 1.11–5.73]; NHL: $RR_{LD} = 4.47$, 95% CI = 1.17–17.1, $RR_{IWLD} = 6.42$ (1.37–30.1), but the risks were slightly lower (between 6–14%) when using the nonexposed referent. When adjusting the baseline analyses for 3 or more hours of sun exposure per day currently or 10 years ago, rate ratios remained elevated and similar to those recorded in Table 2 for all lymphohematopoietic cancers, and NHL (data not shown).

For lung cancer, rate ratios were below 1.00, and exposure-response trends were not statistically significant using nonexposed as the referent. There were nonstatistically significant excess rate ratios observed in both exposure metrics ($RR_{LD} = 1.64$; 95% CI = 0.75–3.61; $RR_{IWLD} = 1.38$; 95% CI = 0.63–3.05) using the low exposed group as the referent. With further stratification by smoking history, rate ratios were null among nonsmokers exposed to butylate and still nonsignificantly increased among those exposed to butylate who had a history of smoking (data not shown). Applicators with the highest exposure to butylate were more similar to the nonexposed referent group on smoking status.

For melanoma, rate ratios were elevated, but not significant for both referent groups for butylate LD (nonexposed: $RR=1.75$, 95%CI = 0.81–3.78; low exposed: $RR = 1.51$, 95% CI

= 0.58–3.92;) and IWLD (nonexposed only: $RR=1.19, 95\%CI=0.50-2.85$), but tests for trends were not significant. Rate ratios decreased for both referent groups, but did not fluctuate by more than 10% when adjusting for ever/never sunlight exposure based on 3 or more hours of sun exposure per day during growing season in the present or 10 years ago.

For colon cancer, we found a statistically significant decreased risk ($RR=0.35, 95\%CI=0.13-0.95$) and exposure response trend using the nonexposed group as the referent ($p=0.04$), but no significant trend using the low exposed group as the referent. For bladder cancer, we found a nonstatistically significant decreased risk and no suggestion of trend using either referent group. For kidney cancer, RRs were essentially null when using the nonexposed referent. Using the low exposed referent, butylate LD ($RR = 1.47, 95\% CI = 0.45-4.85$), but not IWLD ($RR = 0.87, 95\% CI = 0.25-2.99$) was associated with a nonsignificant elevated risk of kidney cancer. When adjusting for ever exposure to two possible kidney carcinogens in both referent groups, asbestos (Pesch et al., 2000; Sali and Boffetta, 2000) and cadmium (Il'yasova and Schwartz, 2005), rate ratios approached the null. For oral cavity cancer, rates were nonstatistically elevated in both referent groups for LD (nonexposed only: $RR=1.15, 95\%CI = 0.70-4.05$) and IWLD (nonexposed: $RR=1.20, 95\%CI=0.88-4.12$; low exposed: $RR = 1.41, 95\% CI = 0.41-4.88$), and tests for trends were not significant. When adjusting this analysis for alcohol use, rates remained the same. Smoking and alcohol use were not significantly associated with oral cavity cancer in our analyses (data not shown).

To further investigate prostate cancer, we stratified by family history of prostate cancer because this was shown to be an important effect modifier in a previous analysis of AHS data (Table 3). Regardless of referent group, a statistically significant elevated risk was seen in the highest exposure categories for those with a prostate cancer family history, and tests for trend were significant (nonexposed: $RR_{LD} = 1.65, 95\% CI = 1.01-2.77, p = 0.04$; $RR_{IWLD} = 1.01-2.78, 95\% CI = 1.07-3.74, p = 0.04$; low exposed: $RR_{LD} = 1.94, 95\% CI = 1.05-3.60$; $RR_{IWLD} = 2.00, 95\% CI = 1.07-3.74$). A statistically significant excess rate ratio was also noted for IWLD for those subjects without a family history of prostate cancer ($RR_{IWLD} = 1.52, 95\% CI = 1.06-2.19$), using low exposed as the referent. Although not significant, interaction terms using both referent groups were elevated.

Discussion

In this study, we examined cumulative lifetime butylate exposure prior to enrollment as a risk factor for incident cancer diagnosed between enrollment and December 2004. In general, we found no statistically significant, consistent associations for lung, leukemia, melanoma, bladder, kidney, and oral cavity cancers, even when adjusting for possible additional confounding factors. However, it should be noted that sample size was small for some cancers. For all cancers, results were inconsistent across referent groups, and the elevated risk in LD seen for those in the higher exposure groups using the low exposed referent was driven primarily by the increased risk of prostate cancer and AL cancers.

We observed a possible association between butylate use and increased prostate cancer risk in our study, particularly for those with a family history of prostate cancer. Previous studies, although not always consistent (Acquavella et al., 1998; Blair et al., 1992), have found the farming occupation (Fleming et al., 1999; Settimi et al., 2001; Settimi et al., 2003; van der Gulden et al., 1995; Van Maele-Fabry et al., 2003) and particularly pesticide exposure, to be modestly but significantly associated with prostate cancer (Morrison et al., 1993; Settimi et al., 2001; van der Gulden et al., 1995). In our study, the exposure-response association using either the LD or the IWLD generally showed an increased prostate cancer risk with increased exposure, though the IWLD was somewhat attenuated. The biological mechanism

linking prostate cancer to pesticide use is not well-understood, though the DNA repair pathways have been implicated (Hu et al. 2004).

Patterns generally were consistent and significant across exposure metrics and across referent groups when evaluating the joint effect of family history and the highest category of butylate use on increased prostate cancer risk. Prostate cancer family history is a known risk factor for prostate cancer (Bratt et al., 1999; Spitz et al., 1991). A statistical interaction between butylate use and a family history of prostate cancer was previously observed in the AHS (Alavanja et al., 2003). Although our interaction terms were elevated, they were not significant. This study has the benefit of longer follow-up time, more detailed butylate exposure information, and the ability to control for additional confounders that could affect the interaction.

We observed a consistent, significant association between butylate exposure, AL cancers, and NHL in our analyses, although the number of exposed cases was small for NHL ($n = 18$) and leukemia ($n = 11$). NHL represented almost half of the reported cases of AL cancers. Previous studies have suggested that exposure to carbamates (Cantor et al., 1992; Hoar et al., 1986; McDuffie et al., 2001; Zahm et al., 1988), thiocarbamates (McDuffie et al., 2001), and butylate specifically (Zheng et al., 2001), may be associated with an elevated risk of NHL. However, studies of molecular mechanisms linking butylate to AL cancers have not been conducted, though chromosomal aberrations have been implicated in linking other pesticides to AL cancers (Baccarelli et al., 2006). Previous studies have also found a possible link between solvent exposure and lymphohematopoietic cancers like multiple myeloma (Sonoda et al., 2005), leukemia (Rushston et al., 1997), and NHL (Fritschi et al., 2005; Kato et al., 2005; Mehlman, 2006). When adjusting for ever/never solvent exposure in our analyses, RRs remained elevated and statistically significant for all lymphohematopoietic cancers and NHL. There is conflicting evidence as to whether exposure to sunlight is positively (Adami et al., 1999) or negatively (Hartge et al., 2006) associated with NHL. In our study, sunlight exposure did not significantly affect the observed rate ratios.

In this analysis, a statistically significant decreased colon cancer risk was seen with increasing butylate exposure for IWLD using the nonexposed as the referent, but the association was not statistically significant when the other exposure metrics or referent group were used. Lack of physical activity is suspected to increase colon cancer risk (Ballard-Barbash et al., 1990; Lee et al., 1997). Farmers are generally believed to have lower mortality rates than the general population because they are physically active (Blair et al., 1991; Blair et al., 1992). Approximately 60% of the applicators in this analysis recorded recreational physical activity of 3–5 hours per week in addition to their physically demanding jobs. When adjusting for physical activity, colon cancer rate ratios were lower.

In this analysis, exposure-response patterns sometimes differed across referent groups and RRs were generally lower for most cancers analyzed when using the nonexposed referent, suggesting that these referent groups may be different due to both identified and unidentified confounding factors among those exposed and unexposed to butylate. With the exception of AL cancers, NHL, and leukemia, RRs were somewhat lower, for the IWLD exposure metric compared to LD. The intensity weighting factor in our exposure metric is designed to help distinguish between exposure days of relatively high exposure from exposure days of relative low exposure. While one would generally expect statistical significance to be more apparent with the more specific exposure metric, i.e., IWLD, some fluctuations of risk estimates may be expected with relatively small samples. When we use the IWLD metric, our sample size reduces slightly from the LD metric, by about 1% across cancers analyzed, so diminished power did not seriously limit our ability to detect differences in cancer risk.

Additionally, when reclassifying the applicators using the IWLD metric, some applicators move from a high exposure group to a lower exposure group or vice versa, which could affect point estimates and tests for trend. Additional follow-up data and exposure data from the AHS cohort incorporating changes in specific pesticide use over time should help further clarify our assessment of cancer risk.

The AHS has several important strengths. It is the largest study to date of pesticide applicators exposed to butylate. Because comprehensive questionnaire data were used to estimate butylate exposure, particularly duration and intensity, we were able to provide greater discrimination between potential high and low exposures to butylate. The AHS has information on many potential cancer risk factors and can control for many potential confounders. In general, farmers provided reliable information and considerable detail regarding their pesticide history (Blair et al., 2002; Hoppin et al., 2002), and in a prospective study like the AHS, the effect of recall bias is minimized as cancers were diagnosed after completing the enrollment questionnaire. Although this study was restricted to the 44% of applicators who completed the supplemental take-home questionnaire, cancer risk was not related to whether applicators did or did not complete the take-home questionnaire, which suggests that collecting information from the take-home questionnaire did not result in selection bias (Tarone et al, 1997).

Certain limitations of our dataset should be recognized including, limited numbers of exposed cancer cases for some analyses, a relatively short period of cancer follow-up, and an exposure assessment that was based primarily on questionnaire data. For example, in a previous analysis, Alavanja et al. 2003 evaluated prostate cancer family history and butylate exposure as ever/never only, using the full cohort (n=55,332). We limited this analysis to those who completed the take-home questionnaire, which included detailed butylate exposure information (n=19,655) in order to evaluate exposure-response associations adjusted for a number of potentially important confounders. The reduced sample size limited our conclusions about some cancers, particularly the effect modification of butylate exposure with a family history of prostate cancer on prostate cancer risk.

Although the period of cancer incidence follow-up is only 9.14 years on average, the actual time from butylate first use to the end of follow-up is longer. Approximately 90% of applicators first used butylate before 1980. Since cancer incidence in the AHS cohort was measured from 1994 through 2004 the minimum period of cancer follow-up for most study subjects would be 14 years for those diagnosed with cancer in 1994, and 24 years for those diagnosed with cancer in 2004, which is a period of time generally thought to encompass the time necessary for the induction of many cancers.

While our exposure assessment was not based on direct measurement of exposure, on every study subject, our IWLD exposure metric is based on questionnaire data that has been shown to be significantly correlated with field measurements of pesticide exposure and should, therefore, generally provide an improved measure of exposure. However, results may vary for individual pesticides (Coble et al. 2005).

With the benefit of a large sample size and detailed exposure information on applicators who personally applied butylate, we observed an association between butylate exposure and all lymphohematopoietic cancers and NHL, which is consistent with previous studies (Cantor et al., 1992; Hoar et al., 1986; McDuffie et al., 2001; Zahm et al., 1988; Zheng et al., 2001). Our findings also suggest a possible association between butylate exposure and prostate cancer incidence and tend to support the previous finding that butylate exposure may be associated with an increased prostate cancer risk in those with a family history of

prostate cancer. It will be important to reevaluate the associations identified in the AHS as new cases accumulate and to compare these results to those in other studies.

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Abbreviations

AHS	Agricultural Health Study
AL	All lymphohematopoietic cancers
CI	Confidence Intervals
EPA	Environmental Protection Agency
ICD-O-2-	International Classification for Disease for Oncology, 2 nd Edition
IRB	Institutional Review Board
IWLD	Intensity-Weighted Lifetime Exposure Day
LD	Lifetime Days of Exposure
NHL	Non-Hodgkin Lymphoma
OR	Odds Ratio
PAN	Pesticide Action Network
RR	Rate Ratios
SIR	Standardized Incidence Ratio

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TABLE 1

Selected Characteristics of Applicators by Butylate Exposure in the Agricultural Health Study Based on 1993–1997 Enrollment Data

Characteristics	Non-exposed group, No. (%) (<i>n</i> = 14368)	Lowest exposed quartile, No. (%) (<i>n</i> = 1668) ¹	Highest 3 quartiles combined, No. (%) (<i>n</i> = 3629) ²
Age			
<40	4538 (31.6)	359 (21.5)	848 (23.4)
40–49	3716 (25.9)	526 (31.5)	1309 (36.0)
50–59	3036 (21.1)	444 (26.6)	884 (24.4)
60	3078 (21.4)	339 (20.4)	588 (16.2)
Sex			
Male	13848(96.3)	1654 (99.2)	3608 (99.4)
Female	520 (3.7)	14 (0.84)	21 (0.58)
Race			
White	14165 (98.6)	1661 (99.6)	3606 (99.4)
Non-white	203 (1.4)	7 (0.40)	23 (0.63)
State of residence			
Iowa	9612 (66.9)	1388 (83.2)	3116 (85.9)
North Carolina	4756 (33.1)	280 (16.8)	513 (14.1)
Applicator type ³			
Private	12756 (88.9)	1606 (96.3)	3147 (86.7)
Commercial	1612 (11.1)	62 (3.7)	482 (13.3)
Smoking history			
Never	8072 (56.1)	985 (59.1)	1994 (55.0)
Low (<12 pack-years)	3121 (21.7)	352 (21.1)	844 (23.2)
High (≥ 12 pack-years)	3175 (22.2)	331 (19.8)	791 (21.8)
Alcohol consumption			
No	5060 (35.2)	466 (27.9)	897 (24.7)
Yes	9308 (64.8)	1202 (72.1)	2732 (75.3)
Educational level			
High school/GED or lower	8098 (56.4)	856 (51.3)	1752 (48.3)
Beyond high school	6270 (43.6)	812 (48.7)	1877 (51.7)
Family history of cancer ⁴			
No	8150 (56.7)	886 (53.1)	1908 (52.6)
Yes	6218 (43.3)	782 (46.9)	1721 (47.4)
Ever exposure to 5 most highly correlated with butylate			
Metribuzin	3933 (26.2) ⁵	1099 (65.9) ⁶	2695 (74.3) ⁷
Chlorimuron-ethyl	4047 (26.9) ⁵	751 (45.0) ⁶	1866 (51.4) ⁷
Pendimethalin	235 4771 (31.7)	808 (48.4) ⁶	2146 (59.1) ⁷
Aldrin	1697 (11.3) ⁵	437 (26.2) ⁶	1027 (28.3) ⁷
Ziram	65 (0.4) ⁵	8 (0.5) ⁶	19 (0.5) ⁷

- ¹First quartile of lifetime days of exposure (years of use × days of use per year).
- ²Second, third and fourth quartile of lifetime days of exposure (years of use X days of use per year).
- ³“Private applicators” refers primarily to individual farmers and “commercial” refers to professional pesticide applicators.
- ⁴Cancer history refers to first degree relatives.
- ⁵Ever exposed to indicated chemical but not to butylate (thus, numbers in columns do not sum to 100%).
- ⁶Ever exposed to indicated chemical and in lowest quartile of butylate exposure (thus, numbers in columns do not sum to 100%).
- ⁷Ever exposed to indicated chemical and in the highest three quartiles of butylate exposure (thus, numbers in columns do not sum to 100%).

TABLE 2

Rate Ratios, 95% Confidence Intervals for Selected Cancers¹ by Lifetime Days and Intensity-Weighted Lifetime Days of Exposure Among Butylate-Exposed² Pesticide Applicator in the Agricultural Health Study

Cancer site/Referent Group LD Cut points	Cancer site/Referent Group			IWL D Cut points		
	N ³	RR _{LD} (95% CI) ⁶	p _{trend} ⁵	N ³	RR _{IWL D} (95% CI) ⁶	p _{trend} ⁵
All cancers						
Non Exposed						
0	924	1.00 (referent)		0	1.00 (referent)	
1-9	94	7 _{0.72} (0.58-0.91)		1-55	7 _{0.79} (0.63-0.99)	
10-25	102	1.00 (0.81-1.23)		56-157	0.83 (0.66-1.06)	
26-56	71	0.97 (0.74-1.26)		158-351	1.12 (0.89-1.42)	
56	78	1.11 (0.87-1.43)	0.39	352	1.00 (0.79-1.26)	0.99
Low Exposed						
1-9	94	1.00 (referent)		1-55	1.00 (referent)	
10-25	102	7 _{1.46} (1.09-1.97)		56-157	0.99 (0.72-1.35)	
26-56	71	7 _{1.60} (1.15-2.21)		158-351	1.36 (1.00-1.86)	
57	78	7 _{1.70} (1.20-2.40)	0.01	352	1.36 (0.97-1.91)	0.15
Prostate						
Non Exposed						
0	390	1.00 (referent)		0	1.00 (referent)	
1-9	40	0.74 (0.53-1.04)		1-55	0.86 (0.61-1.20)	
10-25	49	1.17 (0.87-1.58)		56-157	0.71 (0.48-1.05)	
26-56	25	1.23 (0.58-1.36)		158-351	1.20 (0.90-1.69)	
57	39	7 _{1.44} (1.04-2.00)	0.03	352	1.33 (0.90-1.73)	0.08
Low Exposed						
1-9	40	1.00 (referent)		1-55	1.00 (referent)	
10-25	49 ⁷	1.60 (1.03-2.48)		56-157	0.63 (0.38-1.05)	
26-56	25	1.26 (0.75-2.14)		158-351	1.34 (0.86-2.08)	
57	39	7 _{2.09} (1.27-3.44)	0.004	352	1.47 (0.96-2.26)	0.07

Cancer site/Referent Group			IWLD		
LD Cut points		Cut points			
All lymphohematopoietic					
Non Exposed					
0	76	1.00 (referent)	0	76	1.00 (referent)
1-25	16	0.88 (0.51-1.51)	>0-157	12	0.71 (0.39-1.30)
26	21 7	1.84 (1.14-2.97)	0.01	158	25 71.98 (1.26-3.10)
Low Exposed					
1-25	16	1.00 (referent)	>0-157	12	1.00 (referent)
26	21	72.27 (1.18-4.37)	158	25	73.02 (1.52-6.03)
NHL					
Non Exposed					
0	27	1.00 (referent)	0	27	1.00 (referent)
1-25	6	0.85 (0.35-2.04)	>0-157	5	0.76 (0.29-1.95)
26	12	72.94 (1.49-5.76)	0.002	158	13 72.87 (1.49-5.53)
Low Exposed					
1-25	6	1.00 (referent)	>0-157	5	1.00 (referent)
26	12	73.44 (1.29-9.21)	158	13	73.69 (1.31-10.38)
Leukemia					
Non Exposed					
0	30	1.00 (referent)	0	30	1.00 (referent)
1-25	6	0.83 (0.41-1.70)	>0-157	4	0.70 (0.31-1.54)
26		1.13 (0.51-2.50)	0.76	158	7 1.31 (0.64-2.67)
Low Exposed					
1-25	5	1.00 (referent)	>0-157	4	1.00 (referent)
26	6	2.03 (0.62-6.67)	158	7	2.50 (0.73-8.56)
Lung					
Non Exposed					
0	92	1.00 (referent)	0	92	1.00 (referent)
1-25	12	0.55 (0.30-1.01)	>0-157	12	0.54 (0.29-1.02)
26	13	0.98 (0.54-1.79)	0.96	158	13 0.96 (0.54-1.71)
Low Exposed					

0.89

Cancer site/Referent Group		LD Cut points		IWLD Cut points	
1-25	12	1.00 (referent)		>0-157	12 1.00 (referent)
	13	1.64 (0.75-3.61)		158	13 1.38 (0.63-3.05)
Melanoma					
Non Exposed					
0	34	1.00 (referent)		0	34 1.00 (referent)
1-25	9	1.05 (0.49-2.27)		>0-157	11 1.40 (0.69-2.84)
26	8	1.75 (0.81-3.78)	0.16	158	6 1.19 (0.50-2.85)
Low Exposed					
1-25	9	1.00 (referent)		>0-157	11 1.00 (referent)
26	8	1.51 (0.58-3.92)		158	6 0.80 (0.29-2.16)
Colon					
Non Exposed					
0	74	1.00 (referent)		0	74 1.00 (referent)
1-25	12	0.60 (0.32-1.12)		>0-157	14 0.76 (0.42-1.36)
26	6	0.57 (0.25-1.32)	0.19	158	4 70.35 (0.13-0.94)
Low Exposed					
1-25	12	1.00 (referent)		>0-157	14 1.00 (referent)
26	6	0.89 (0.33-2.37)		158	4 0.43 (0.14-1.32)
Bladder					
Non Exposed					
0	38	1.00 (referent)		0	38 1.00 (referent)
1-25	12	0.45 (0.30-2.01)		>0-157	14 0.56 (0.47-1.46)
26	6	0.59 (0.35-1.89)	0.60	158	4 0.61 (0.23-1.67)
Low Exposed					
1-25	13	1.00 (referent)		>0-157	13 1.00 (referent)
26	5	0.62 (0.22-1.75)		158	5 0.52 (0.18-1.46)
Kidney					
Non Exposed					
0	23	1.00 (referent)		0	23 1.00 (referent)
1-25	6	1.01 (.85-2.01)		>0-157	6 1.04 (.71-3.02)
26	5	1.12 (0.78-4.85)	0.71	158	5 1.01 (0.87-4.10)

Cancer site/Referent Group LD Cut points	IWLD Cut points		
Low Exposed			
1–25	6	1.00 (referent)	>0–157 6 1.00 (referent)
26	5	1.47 (0.45–4.85)	158 5 0.87 (0.25–2.99)
Oral cavity			
Non Exposed			
0	21	1.00 (referent)	0 21 1.00 (referent)
1–25	6	0.90 (.85–2.15)	>0–157 6 0.78 (.67–2.02)
26	5	1.15 (0.70–4.05)	0.51 > 158 5 1.20 (0.88–4.12)
0.63			
Low Exposed			
1–25	6	1.00 (referent)	>0–157 5 1.00 (referent)
26	4	1.07 (0.30–3.82)	158 5 1.41 (0.41–4.88)

¹ Cancers for which there at least 10 exposed cases. Rate ratios adjusted for age, sex, race, education, smoking status and family history of cancer.

² Total number exposed to butylate without pre-cancer history prior to enrollment and missing exposure information = 5,497.

³ Number of cancer-specific case patients exposed to butylate (total and for each quartile or low/high exposure level).

⁴ $RR_{[d]}$ = rate ratio of lifetime days of exposure (i.e., years of use $\times$ number of days of use per year).

⁵ p values were two-sided.

⁶ $RR_{[IWLD]}$ = rate ratio of intensity weighted lifetime days of exposure (i.e., years of use $\times$ number of days of use per year $\times$ intensity index).

⁷ Indicates statistical significance.

Rate Ratios and 95% Confidence Intervals for Prostate Cancer Family History and Butylate Exposure Among Pesticide Applicators in the Agricultural Health Study¹

TABLE 3

Non-Exposed Referent									
No Family History			Family History			Interaction ²			
Cases (n)	RR	CI	Cases (n)	RR	CI	RR	CI	RR	CI
Lifetime Exposure-Days									
0	349	1.00	Ref	74	1.00	Ref			
>0-25	72	0.94	0.72-1.21	17	0.95	0.57-1.60			
26+	44	0.93	0.66-1.30	20	1.65 ³	1.01-2.77	1.75	0.95-3.04	
P _{TREND} [§]		0.67			0.04				
Intensity-Weighted Exposure-Days									
0	349	1.00	Ref	74	1.00	Ref			
>0-157	58	0.80	0.60-1.07	17	0.93	0.55-1.58			
+158	56	1.10	0.81-1.48	20	1.67 ³	1.01-2.78	1.34	1.00-1.76	
P _{TREND} [§]		0.55			0.04				
Low exposed referent									
No family history			Family history			Interaction ²			
Cases (n)	RR	CI	Cases (n)	RR	CI	RR	CI	RR	CI
Lifetime exposure-days									
>0-25	72	1.00	Ref	17	1.00	Ref			
26+	44	1.12	0.77-1.64	20	1.94 ³	1.05-3.60	1.79	0.87-3.67	
Intensity-weighted exposure-days									
>0-157	58	1.00	Ref	17	1.00	Ref			
+158	56	1.52 ³	1.06-2.19	20	2.00 ³	1.07-3.74	1.37	0.67-2.80	

¹ Adjusted by age, race, sex, education, smoking status.

² Interaction term = cross-product of family history of prostate cancer and the highest lifetime exposure days metric, adjusted by age, race, education, smoking status, family history of prostate cancer.

³ Indicates statistical significance.