Published in final edited form as:

Cancer Causes Control. 2012 June ; 23(6): 807–818. doi:10.1007/s10552-012-9949-2.

Methyl bromide exposure and cancer risk in the Agricultural Health Study

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Abstract

Purpose—Methyl bromide is a genotoxic soil fumigant with high acute toxicity, but unknown human carcinogenicity. Although many countries have reduced methyl bromide use because of its ozone depleting properties, some uses remain in the United States and other countries, warranting further investigation of human health effects.

Methods—We used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (CI) for associations between methyl bromide use and all cancers combined and 12 specific sites among 53,588 Agricultural Health Study (AHS) pesticide applicators with follow-up from 1993–2007. We also evaluated interactions with a family history for four common cancers (prostate, lung, colon, and lymphohematopoietic). We categorized methyl bromide exposure based on lifetime days applied weighted by an intensity score.

Results—A total of 7,814 applicators (14.6%) used methyl bromide, predominantly before enrollment. Based on 15 exposed cases, stomach cancer risk increased monotonically with increasing methyl bromide use (RR=1.42; 95% CI: 0.51–3.95 and RR=3.13; 95% CI: 1.25–7.80 for low and high use compared with no use; $p_{\text{trend}}=0.02$). No other sites displayed a significant monotonic pattern. Although we previously observed an association with prostate cancer (follow-up through 1999), the association did not persist with longer follow-up. We observed a non-significant elevated risk of prostate cancer with methyl bromide use among those with a family history of prostate cancer, but the interaction with a family history did not achieve statistical significance.

Conclusions—Our results provide little evidence of methyl bromide associations with cancer risk for most sites examined; however, we observed a significant exposure-dependent increase in stomach cancer risk. Small numbers of exposed cases and declining methyl bromide use might have influenced our findings. Further study is needed in more recently exposed populations to expand on these results.

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Conflict of interest

The authors declare that they have no conflict of interest.

Keywords

methyl bromide; fumigant; pesticide; cancer

INTRODUCTION

Methyl bromide, also known as bromomethane, is most commonly used in the United States as a soil fumigant for crops such as tomatoes and strawberries to control various pests. Other uses include application as a post-harvest pesticide for agricultural commodities and as a treatment for imported commodities [1]. Historically, methyl bromide was also used in structural fumigation and as a methylating agent in organic synthesis [2]. Although methyl bromide use in the United States declined from 1993–2005 due to a U.S. EPA phaseout in accordance with the Montreal Protocol and Clean Air Act because of its ozone depleting properties, some use remains in the United States from allowable exemptions [3], as well as in other countries [4]. While the phaseout in developed countries under the Montreal Protocol has already been completed, the phaseout in developing countries is expected by 2015 [5]. Due to concerns about methyl bromide inhalation exposures to handlers, other agricultural workers, and bystanders because of the chemical's volatility, the latest U.S. EPA reregistration eligibility decision for soil and structural uses of methyl bromide required a number of mitigation measures (e.g. buffer zones around application sites) [1]. As an EPA Toxicity Class I chemical, methyl bromide is considered highly toxic to humans. Consequences of exposure can include acute toxicity to the nervous system and lungs, which can lead to organ system failure and death, and residual defects, such as persistent neurological effects [2]. However, the carcinogenicity of methyl bromide has been little studied in humans. While the National Institute for Occupational Safety and Health (NIOSH) lists methyl bromide as a potential occupational carcinogen [6], IARC ranks its carcinogenicity as unknown (group 3) [7].

There is evidence for a carcinogenic potential of methyl bromide based on its known genotoxic activity. Methyl bromide has been shown to induce DNA adducts (3-methyl-adenine, 7-methyl-guanine, and O⁶-methyl-guanine) in the liver, lung, stomach, and forestomach of exposed rats [8] by donating methyl groups that bind covalently to DNA bases. In addition, methyl bromide exposure has been associated with increased mutations and sister chromatid exchanges *in vitro* and increased micronuclei formation in the bone marrow and peripheral blood cells of exposed rodents [7]. In humans, a small cross-sectional study of methyl bromide fumigation workers observed borderline significant increases in lymphocyte hypoxanthine-guanine phosphoribosyl transferase gene (hprt) mutations and oropharyngeal cell micronuclei [9].

Some rodent bioassays have observed an increased risk of forestomach carcinomas or adenomas of the pituitary gland with methyl bromide exposure, but studies have been inconsistent, and IARC has concluded that the evidence in experimental animals for the carcinogenicity of methyl bromide is limited [7]. The few epidemiologic studies of methyl bromide and cancer outcomes suggest possible associations with prostate, stomach, and testicular cancers [10–14]. A prostate cancer case-control study in the U.S. Agricultural Health Study (AHS), a prospective cohort of pesticide applicators in Iowa and North Carolina, detected increased prostate cancer risk associated with methyl bromide use based on cancer follow-up through 1999 [odds ratio (OR) for the highest exposure category compared with the non-exposed group = 3.47; 95% confidence interval (CI): 1.37–8.76; $p_{\text{trend}} = 0.008$] [10]. In addition, two prostate cancer case-control studies in California suggested increased risk associated with occupational exposure (OR for the highest compared with the lowest exposure group = 1.59; 95% CI: 0.77–3.30) [11] or ambient

exposure (OR for any exposure compared with no exposure = 1.62, 95% CI: 1.02–2.59) [12]. A case-control study of stomach cancer in California observed increased risk associated with the highest tertile of occupational exposure using the lowest tertile as the referent group, but not using the non-exposed group as the referent (OR = 2.38, 95% CI: 1.06–5.37 and OR = 1.33, 95% CI: 0.67–2.67, respectively) [13]. An earlier cohort study of white male workers with potential exposure to organic brominated compounds, including methyl bromide, at three chemical manufacturing plants and a research establishment in the U.S. suggested an excess of testicular cancer deaths, although based on only two deaths [14].

In the present analysis, we investigated the relationship between methyl bromide use and risk of a number of cancer sites among pesticide applicators in the AHS. Since a family history of cancer might serve as a proxy for an inherited genetic susceptibility to developing cancer, we also evaluated interactions between methyl bromide use and a family history of cancers where numbers allowed.

METHODS

Study population

The AHS cohort has been described in detail elsewhere [15]. Briefly, 57,310 licensed restricted-use pesticide applicators in Iowa and North Carolina and 32,346 of their spouses were enrolled between December 1993 and December 1997. All participants provided informed consent, and the protocol was approved by all appropriate Institutional Review Boards. Participants are linked annually to the Iowa and North Carolina state cancer registries to ascertain cancer diagnoses and to state death registries and the National Death Index to ascertain vital status. Person-years at risk were calculated for each participant starting at the date of cohort enrollment and ending at the date of first incident cancer diagnosis, death, loss to follow-up, or December 31, 2007, whichever occurred first. Loss to follow-up was largely due to out-migration from Iowa and North Carolina; for these participants, person-years were censored at the date of exit from the state (based on IRS record). We conducted the present analysis among pesticide applicators in the AHS and excluded those with a cancer diagnosis prior to enrollment (except for non-melanoma skin cancers), $n=1,094$, those who did not contribute any person-years of follow-up, $n=272$, and those missing data needed to characterize methyl bromide exposure, $n=2,356$, resulting in a final sample size of 53,588 pesticide applicators. Among these applicators, 7,814 (14.6%) reported any use of methyl bromide. The median length of follow-up was 12.3 years.

Exposure assessment

Information on lifetime use of 50 pesticides was captured in two self-administered questionnaires (<http://aghealth.org/questionnaires.html>) completed during cohort enrollment (Phase 1, from 1993–1997) and an interviewer-administered follow-up telephone questionnaire (Phase 2, from 1999–2005). All 57,310 AHS applicators completed the first enrollment questionnaire, which inquired about ever/never use of the 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides, including methyl bromide. In addition, 25,291 (44.1%) of the applicators returned the second (take home) enrollment questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides.

Of the 57,310 applicators, 36,342 (63.4%) responded to the Phase 2 computer-assisted telephone interview (CATI), which inquired about crops raised, as well as each pesticide used and its frequency of use in the most recent year of farming (reference year). Frequency

of pesticide application in the reference year was used to estimate pesticide use for the years between enrollment and the reference year.

We combined Phase 1 and 2 data to compute two cumulative exposure metrics for methyl bromide, lifetime days of application (years x days/year applied) and intensity-weighted lifetime days (lifetime days x intensity score). The intensity score was derived from an algorithm based on mixing status, application method, equipment repair, and use of personal protective equipment [16] that was recently updated [17]. We also generated lagged variables, which discounted the most recent 15 years of exposure, because recent exposures might not be relevant to diseases expected to have a long latency, such as many cancers. Pesticide data for the present analysis were obtained from AHS data release versions P1REL201005.00 (for Phase 1) and P2REL201007.00 (for Phase 2).

Since there were very few new users of methyl bromide at Phase 2, we minimized the number of applicators with missing Phase 2 values for methyl bromide by assuming that participants who reported no use of methyl bromide prior to enrollment and did not provide Phase 2 information (because of questionnaire non-response or failure to answer specific items about methyl bromide on the questionnaire) never used methyl bromide. In our final sample of 53,588 applicators, only 19 reported no use of methyl bromide prior to enrollment, but then reported use on the Phase 2 questionnaire. This contrasts with the 29,325 applicators who reported no use prior to enrollment and no use in Phase 2. For applicators who reported use of methyl bromide prior to enrollment and did not provide Phase 2 information, we assigned methyl bromide exposure based on the information reported in Phase 1. Figure 1 describes the treatment of missing methyl bromide data in our population, including exclusion of some participants for whom we did not conduct imputation, as well as other exclusions that we made to arrive at our final sample.

We expect that our approach based on the fixed assumptions described above might have resulted in some underestimation of lifetime methyl bromide use (i.e. for participants who did not respond to Phase 2, but continued to use methyl bromide at that time or started using methyl bromide between Phase 1 and Phase 2). Thus, we compared results using this approach with results derived from a multiple imputation for missing pesticide use in Phase 2 due to questionnaire non-response (any use and days/year applied for each pesticide), which has been previously described [18]. Findings were similar for the two methods, and we do not present results based on the multiple imputation; however, results based on the multiple imputation for a number of pesticides, including methyl bromide, with prostate cancer risk have been described elsewhere (Koutros et al, in press). The similarity in findings was expected given the marked decline in methyl bromide use in the cohort (of the 34,371 Phase 2 responders in our sample, 5,043, or 14.7%, reported any use, 1,456, or 4.2%, reported use in the past year at enrollment, and 181, or 0.5%, reported use at Phase 2), such that a small percentage of Phase 2 non-responders was expected to be using methyl bromide at Phase 2.

Statistical analysis

We used Poisson regression to compute rate ratios (RR) and 95% confidence intervals (CI) for the associations between methyl bromide use and all cancers combined, as well as the 12 specific cancer sites with at least 15 methyl bromide-exposed cases: prostate, stomach, lymphohematopoietic [which includes non-Hodgkin lymphoma (NHL), leukemia, Hodgkin lymphoma, and multiple myeloma], NHL, leukemia, oral cavity, colon, rectum, lung, bladder, kidney, and melanoma.

We categorized the methyl bromide exposure metrics into tertiles based on the distribution among exposed cancer cases (all cancers combined), and further divided the upper category

at the median (cutpoints at the 33rd, 67th, and 83rd percentiles), resulting in a 5-level variable with the non-exposed group as the referent. We also generated 3-level and 4-level categorical exposure variables for use with rarer cancers with the non-exposed group as the referent, based on exposure categories using medians or tertiles as cutpoints. For analysis, we required at least five exposed cancer cases within each exposure category. Thus, we used the five-level variable for all cancers combined, as well as prostate, lymphohematopoietic, colon, rectum, and lung cancers, the four-level variable for NHL, leukemia, bladder cancer, kidney cancer, and melanoma, and the three-level variable for stomach and oral cavity cancers. For testing linear trend, we generated continuous score variables using the median value for each category. We observed similar results for the intensity-weighted and unweighted exposure metrics and present only the former.

For a subgroup of cancers where numbers allowed (prostate, lung, colon, and lymphohematopoietic), we evaluated interactions between methyl bromide use and a first-degree family history of the specific cancer using likelihood ratio tests (LRT) comparing nested models with and without the interaction terms. All analyses were conducted using SAS, version 9.1 (SAS Institute, Cary, NC).

We adjusted all models for the following covariates using Phase 1 information (including a category for missing if applicable): attained age (less than 50, 50–59, 60 or older), gender, race (white, non-white, missing), state of residence (Iowa, North Carolina), applicator type (private, commercial), enrollment year (1993–1997), cigarette smoking status (never, former, current, missing), alcohol consumption in the past 12 months at enrollment (yes, no, missing), education (high school or less, high school graduate or GED, more than high school, missing), and family history of cancer (yes, no, missing), using family history of the specific type of cancer where available: for prostate, stomach, lymphohematopoietic (based on family history of leukemia or lymphoma), leukemia, NHL, colon, lung, and melanoma. When a family history of the specific cancer was not available, we adjusted for a family history of any cancer. We selected these covariates for adjustment because they were thought to be associated with cancer risk based on the literature. Additionally, we adjusted models for ever/never use (using Phase 1 and 2 information) of the five pesticides that were most highly correlated with intensity-weighted days of methyl bromide use (Spearman rho: 0.35–0.60): metalaxyl, ethylene dibromide, carbaryl, aldicarb, and maneb/mancozeb.

RESULTS

Table 1 presents the distribution of person-years of follow-up for various demographic, lifestyle and occupational factors by cumulative methyl bromide use (none, low, and high, with low and high defined based on the median intensity-weighted lifetime days). The distribution of person-years significantly varied by methyl bromide use for all of these factors (data not shown); however, some of the differences were small and likely achieved significance because of the large sample size and relatively long follow-up in our study. Methyl bromide was used more frequently by participants in North Carolina. In addition, participants with higher methyl bromide use tended to be older and to have enrolled earlier, and were more frequently private applicators, former/current smokers, non-drinkers, and applicators of the five most correlated pesticides with methyl bromide when compared with participants with lower methyl bromide use (Table 1).

With follow-up through 2007 and with 280 exposed cases, there was no suggestion of increasing risk of prostate cancer with increasing methyl bromide use ($p_{\text{trend}} = 0.90$) (Table 2). This contrasts with a previous analysis of prostate cancer in the AHS with follow-up through 1999, which observed a significant trend based on 67 exposed cases [10]. We observed a significant monotonic increase in the risk of stomach cancer with increasing

methyl bromide use based on 15 exposed cases (RR=1.42; 95% CI: 0.51–3.95 and RR=3.13; 95% CI: 1.25–7.80 for low and high use compared with no use, respectively; $p_{\text{trend}}=0.02$). No other cancer sites displayed a significant monotonic pattern with increasing methyl bromide use (Table 2).

We observed similar patterns for all sites using exposure metrics that encompassed a 15-year lag (Table 2). In addition, results were similar for North Carolina residents only (Iowa could not be examined separately due to small numbers of exposed cases), Phase 1 exposure data only, and participants who completed both Phase 1 and 2 questionnaires (data not shown).

Because a previous AHS analysis observed an association for methyl bromide and prostate cancer [10], whereas we did not with additional follow-up, we computed RRs for prostate cancer within categories of calendar year of follow-up. Although we did not observe significant variation in the RRs by calendar time (LRT p -value for interaction = 0.81; data not shown), we observed a non-significant elevated risk of prostate cancer for the highest exposure category (18 exposed prostate cancer cases) compared with the non-exposed group with follow-up from 1993–1998 (RR=1.52; 95% CI: 0.90–2.59) that diminished over time. Figure 2 illustrates this pattern based on the negative slope for the fitted trend over time on a log-linear scale. When we compared characteristics of the prostate cancer cases diagnosed between 1993 and 1998 to the later diagnosed cases (1999–2007), we found that the later diagnosed cases were younger at enrollment (average ages for the earlier and later diagnosed cases were 63.4 and 58.2 years, respectively; t -test p -value < 0.0001) and also had lower cumulative methyl bromide use (average intensity-weighted lifetime days for the earlier and later diagnosed cases were 945.9 and 397.4, respectively; t -test p -value = 0.02).

We also examined associations between methyl bromide and other cancer sites by calendar time of follow-up to assess whether these associations were increased earlier in follow-up as for prostate cancer, although numbers of exposed cases became very small for most of the sites and further constrained the number of exposure categories we could examine (data not shown). We did not observe a significant monotonic pattern for any cancer site with follow-up from 1993–1998; however, for some sites we were limited to evaluate ever/never methyl bromide use and therefore could not assess the pattern in risk with increasing use.

We observed a borderline significant interaction between any methyl bromide use and a family history of prostate cancer, but not for a family history of the other cancers examined (p_{interact} = 0.05, 0.44, 0.19, and 0.67 for prostate, lung, colon, and lymphohematopoietic cancers, respectively) (Table 3). Our findings suggested an increase in prostate cancer risk among participants with a family history (RR for any use compared with no use = 1.46; 95% CI: 0.97–2.20), in contrast to no association among participants without a family history (RR = 0.91; 95% CI: 0.75–1.10). However, when we evaluated more categories of methyl bromide use, we did not observe a significant interaction (p_{interact} = 0.19) or an exposure-response relationship among those with a family history (Table 3).

DISCUSSION

Our analysis of associations between methyl bromide use and risk of all cancers combined and 12 specific cancer sites among pesticide applicators in the AHS with follow-up from 1993 through 2007 found no significant monotonic associations, except for stomach cancer, which was based on 15 exposed cases. We did not observe an association between methyl bromide and prostate cancer over the full follow-up period. However, we observed an increased risk of prostate cancer associated with high methyl bromide use in an early period of follow-up (1993–1998), consistent with a previous report in the AHS, that diminished over time. Our findings provided some evidence of an increase in prostate cancer risk with

methyl bromide use among participants with a family history of prostate cancer in contrast to no association among those without a family history, but the interaction did not achieve statistical significance and there was no exposure-response relationship among those with a family history. We did not observe evidence of an interaction between methyl bromide and a family history of lung, colon, or lymphohematopoietic cancers.

Although our finding of an association between methyl bromide and stomach cancer may be due to chance, our finding is consistent with a California case-control study of stomach cancer, which observed a more than two-fold increase in risk associated with the highest compared with the lowest tertile of exposure [13]. In addition, there is some biological plausibility for an association with stomach cancer. DNA adducts have been isolated from the stomach and forestomach of rats with oral or inhalation exposure to methyl bromide [8], and other studies in rats have observed increased formation of hyperplastic and neoplastic lesions in the forestomach with oral exposure to methyl bromide by gavage [19, 20]. However, regression of the lesions following cessation of exposure raised uncertainty about the malignant nature of the lesions [20], and the relevance of rodent forestomach carcinogenesis to human cancer risk has also been questioned [21]. In addition, other studies in rats, using different routes of exposure, observed no evidence of methyl bromide carcinogenicity [22, 23].

Similar to a previous analysis of prostate cancer in the AHS with follow-up through 1999, which used different cutpoints for categorizing methyl bromide [10], our findings suggested an increase in prostate cancer risk associated with methyl bromide for an early period of follow-up (1993–1998). Our results are consistent with findings from a nested case-control study among Hispanic farmworkers in California [11], which followed participants through 1999. However, a population-based case-control study of prostate cancer in California [12], which estimated exposure based on residential proximity to crop application of methyl bromide, observed increased prostate cancer risk for more recently diagnosed cases (2005–2006). Based on 1997 estimates, the highest methyl bromide use (pounds of active ingredient) in the United States occurred in California [24]. More recent methyl bromide use in California compared with the AHS study region could potentially explain why the California case-control study based on diagnoses from 2005–2006 observed an association with prostate cancer, whereas we did not for recent years. In the AHS, most participants had already stopped using methyl bromide by the time of study enrollment (1993–1997), although information on specific time of cessation was not available. It is possible that the early association between methyl bromide and prostate cancer in our study was real and became diluted with continued follow-up because of the increasing time since the occurrence of exposure. We also found that the AHS prostate cancer cases diagnosed later in follow-up (1999–2007) had lower cumulative methyl bromide use compared with those diagnosed earlier (1993–1998). Thus, adding the later diagnosed cases would tend to weaken any methyl bromide association. However, it is equally possible that the early association in our study was due to chance.

A previous study among methyl bromide fumigation workers observed increased hypoxanthine-guanine phosphoribosyl transferase gene (hprt) mutations in lymphocytes and increased micronuclei formation in oropharyngeal cells [9], which suggested a carcinogenic potential of methyl bromide with respect to hematopoietic and oropharyngeal cells. In the present study, we were unable to examine oropharyngeal cancers alone because of small numbers; however, we found little evidence of increased risk for a group of cancers in the oral cavity region, which included oropharyngeal cancers. Our findings also provided little evidence of an association between methyl bromide and lymphohematopoietic cancers. Although we observed a significant elevation in the risk of lymphohematopoietic cancers combined, as well as NHL specifically, associated with exposure in the lowest tertile

(compared with the non-exposed group), the risk did not continue to increase with increasing exposure. In addition, the elevated risk did not persist when we evaluated any compared with no methyl bromide use (data not shown).

Despite the large overall sample size, infrequent use of methyl bromide resulted in relatively small numbers of exposed cases for most of the cancers, and therefore limited power to detect associations (particularly for rarer cancers). Additionally, small numbers precluded our ability to evaluate some cancers, including testicular cancer, which was of interest based on findings from a cohort of potentially exposed workers [14]. We also expect some exposure misclassification in our study [25], as with any study using self-reported information; however, the prospective design reduced the potential for recall or reporting bias to influence our results, and self-reported pesticide information in the AHS has been demonstrated to be reliable and consistent with the dates of introduction to the market [26, 27].

Our study had several strengths. The participation rate was high, with about 82% of the target applicator population enrolled, and there has been minimal loss to cancer follow-up (2.2% as of January 2012) in the cohort. As a cohort study, we were able to assess pesticide use prior to disease occurrence, as well as to assess exposures over time, although use of methyl bromide tended to decline over time. We focused our analyses on the intensity-weighted exposure metric, which incorporates an intensity score that has shown moderate correlation with biomarkers of pesticide exposure in post-application urine samples; however, methyl bromide has not been specifically evaluated [28].

In summary, in this population of primarily white male private applicators in the AHS with follow-up from 1993 through 2007, we observed little evidence of associations between methyl bromide and most cancers examined; however, there were small numbers of exposed cases for many sites. Our finding of a significant monotonic increase in stomach cancer risk with increasing methyl bromide use is supported by a previous report of increased stomach cancer risk associated with methyl bromide in a California case-control study, as well as some experimental animal findings. This association warrants re-evaluation in the AHS with longer follow-up, as well as examination in other epidemiologic studies. Although we previously observed an association with prostate cancer in the AHS (follow-up through 1999), the association did not persist with longer follow-up. We observed a non-significant elevated risk of prostate cancer with methyl bromide use among those with a family history of prostate cancer, but the interaction with a family history did not achieve statistical significance. It is unclear whether the early finding with prostate cancer in the AHS was due to chance or whether the finding was real and potentially attenuated with continued follow-up due to diminishing methyl bromide use over time. With the declining use of methyl bromide worldwide, there are limited opportunities for further study; however, there is some potential for future work in developing countries because of the delayed phaseout in these countries, as well as areas in developed countries (e.g. California) where methyl bromide is still in use.

Acknowledgments

This research was supported by the Intramural Research Program of the National Cancer Institute, Division of Cancer Epidemiology and Genetics (Z01CP010119), and National Institute of Environmental Health Sciences (Z01ES049030), National Institutes of Health. Additionally, support for K.H.B. was provided by National Cancer Institute grant T32 CA105666.

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Starting N = 57,310 applicators*

Fig. 1.

Study exclusions and treatment of missing methyl bromide data

*Abbreviations: IW days, intensity-weighted lifetime days; MB, methyl bromide

Fig. 2.

Effect modification of the association between high methyl bromide use (upper half of tertile 3 of intensity-weighted lifetime days compared with no methyl bromide use) and prostate cancer risk by calendar time of follow-up among male pesticide applicators in the Agricultural Health Study, adjusted for age, race, state of residence, applicator type, enrollment year, cigarette smoking status, alcohol consumption, education, family history of prostate cancer, and ever/never categorizations of the five pesticides most highly correlated with methyl bromide: metalaxyl, ethylene dibromide, carbaryl, aldicarb, and maneb/mancozeb

*generated using Origin software (OriginLab Corporation, Northampton, MA)

Table 1

Total person-years of follow-up for various demographic, lifestyle, and occupational factors by cumulative methyl bromide exposure (none, low, high) among pesticide applicators in the Agricultural Health Study, with follow-up from 1993–2007^a

Characteristic	No exposure		Low ^b		High ^b	
	Person-years (total=538,474) [*]	%	Person-years (total=48,539) [*]	%	Person-years (total=44,010) [*]	%
Attained age (years)						
<50	278,245	51.7	23,651	48.7	18,473	42.0
50–59	128,137	23.8	11,684	24.1	11,976	27.2
60 or older	132,092	24.5	13,205	27.2	13,562	30.8
Gender						
Male	523,538	97.2	47,018	96.9	43,436	98.7
Female	14,936	2.8	1,521	3.1	574	1.3
Race						
White	524,961	97.5	46,462	95.7	42,508	96.6
Non-white	12,342	2.3	1,949	4.0	1,371	3.1
Missing	1,172	0.2	128	0.3	131	0.3
State						
Iowa	408,959	75.9	5,510	11.4	1,108	2.5
North Carolina	129,515	24.1	43,030	88.7	42,902	97.5
Applicator type						
Private	483,330	89.8	47,365	97.6	43,528	98.9
Commercial	55,144	10.2	1,174	2.4	481	1.1
Year of enrollment						
1993	5,207	1.0	80	0.2	28	0.1
1994	197,896	36.8	19,523	40.2	18,836	42.8
1995	137,730	25.6	15,211	31.3	14,316	32.5
1996	154,562	28.7	12,513	25.8	10,610	24.1
1997	43,079	8.0	1,212	2.5	220	0.5
Cigarette smoking status						
Never	300,303	55.8	20,833	42.9	16,169	36.7
Former	149,736	27.8	16,681	34.4	15,887	36.1

Characteristic	No exposure		Low ^b		High ^b	
	Person-years (total=538,474)*	%	Person-years (total=48,539)*	%	Person-years (total=44,010)*	%
Current	83,361	15.5	10,554	21.7	11,518	26.2
Missing	5,073	0.9	471	1.0	436	1.0
Alcohol consumption (past year) ^c						
No	146,053	27.1	22,518	46.4	21,568	49.0
Yes	373,128	69.3	22,971	47.3	20,317	46.2
Missing	19,293	3.6	3,051	6.3	2,124	4.8
Education						
High school or less	42,373	7.9	5,744	11.8	5,327	12.1
High school graduate or GED	254,304	47.2	19,817	40.8	20,382	46.3
More than high school	231,655	43.0	21,702	44.7	17,143	39.0
Missing	10,142	1.9	1,276	2.6	1,157	2.6
Family history of any cancer ^d						
No	301,552	56.0	24,415	50.3	22,105	50.2
Yes	204,847	38.0	19,357	39.9	17,654	40.1
Missing	32,075	6.0	4,767	9.8	4,251	9.7
Other pesticides used						
Metalaxyl						
Ever	79,619	14.8	31,348	64.6	35,885	81.5
Never	288,379	53.6	9,446	19.5	3,759	8.5
Missing	170,477	31.7	7,745	16.0	4,366	9.9
Ethylene dibromide						
Ever	10,993	2.0	8,386	17.3	9,665	22.0
Never	332,453	61.7	23,276	48.0	19,470	44.2
Missing	195,028	36.2	16,877	34.8	14,874	33.8
Carbaryl						
Ever	268,238	49.8	39,163	80.7	37,499	85.2
Never	155,156	28.8	3,765	7.8	2,382	5.4
Missing	115,080	21.4	5,611	11.6	4,129	9.4
Aldicarb						
Ever	42,253	7.8	14,212	29.3	17,313	39.3

Characteristic	No exposure		Low ^b		High ^b	
	Person-years (total=538,474) [*]	%	Person-years (total=48,539) [*]	%	Person-years (total=44,010) [*]	%
Never	315,312	58.6	20,717	42.7	15,611	35.5
Missing	180,910	33.6	13,610	28.0	11,086	25.2
Maneb/mancozeb						
Ever	33,296	6.2	13,632	28.1	15,340	34.9
Never	318,103	59.1	19,823	40.8	16,185	36.8
Missing	187,075	34.7	15,085	31.1	12,485	28.4
Median person-years of follow-up (25th: 75th percentiles)	12.1 (11.5: 13.3)		12.8 (11.8: 13.8)		12.8 (11.8: 13.8)	

^{*} Person-years may not sum to column totals due to rounding

^a Excludes applicators with a cancer diagnosis (except non-melanoma skin cancers) prior to cohort enrollment, applicators that did not contribute any person-years of follow-up, and applicators with missing data to characterize methyl bromide exposure

^b Low and high methyl bromide use defined by the median intensity-weighted lifetime days of methyl bromide application among exposed cancer cases (all cancers combined)

^c Reported alcohol consumption within the last 12 months at enrollment

^d Family history of any cancer in a first-degree relative

Table 2

Intensity-weighted lifetime days of methyl bromide application and risk of various cancers among pesticide applicators in the Agricultural Health Study, with follow-up from 1993–2007

Intensity-weighted lifetime days	No. of cases	RR ^a	95% CI ^a	Intensity-weighted lifetime days, 15-year lag ^b	No. of cases	RR ^a	95% CI ^a
All cancers							
0	3,854	1.00	REF	0	3,972	1.00	REF
>0–310	264	1.08	0.95–1.24	>0–275	222	1.07	0.93–1.24
>310–1,519	263	0.86	0.75–0.98	>275–1,323	223	0.84	0.72–0.97
>1,519–4,032	130	0.84	0.70–1.02	>1,323–3,564	110	0.82	0.68–1.01
>4,032	129	1.05	0.86–1.26	>3,564	111	1.04	0.85–1.27
P_{trend}^c		0.96		P_{trend}^c		0.86	
Prostate cancer ^d							
0	1,571	1.00	REF	0	1,611	1.00	REF
>0–310	82	0.90	0.71–1.14	>0–275	75	0.97	0.76–1.23
>310–1,519	106	0.96	0.77–1.19	>275–1,323	85	0.87	0.68–1.10
>1,519–4,032	48	0.86	0.63–1.17	>1,323–3,564	39	0.79	0.56–1.10
>4,032	44	0.99	0.72–1.36	>3,564	40	1.01	0.72–1.41
P_{trend}^c		0.90		P_{trend}^c		0.81	
Stomach cancer							
0	51	1.00	REF	0	52	1.00	REF
>0–765	5	1.42	0.51–3.95	>0–661.5	5	1.71	0.61–4.77
>765	10	3.13	1.25–7.80	>661.5	9	3.33	1.30–8.51
P_{trend}^c		0.02		P_{trend}^c		0.02	
Lymphohematopoietic cancers							
0	360	1.00	REF	0	373	1.00	REF
>0–310	33	1.60	1.08–2.37	>0–275	24	1.38	0.89–2.15
>310–1,519	20	0.77	0.47–1.27	>275–1,323	14	0.63	0.36–1.11
>1,519–4,032	8	0.63	0.30–1.30	>1,323–3,564	11	0.99	0.53–1.88
>4,032	7	0.72	0.33–1.58	>3,564	6	0.73	0.31–1.69
P_{trend}^c		0.17		P_{trend}^c		0.38	

Intensity-weighted lifetime days	No. of cases	RR ^a	95% CI ^a	Intensity-weighted lifetime days, 15-year lag ^b	No. of cases	RR ^a	95% CI ^a
NHL							
0	166	1.00	REF	0	174	1.00	REF
>0-310	21	2.33	1.40-3.88	>0-275	13	1.67	0.91-3.07
>310-1,519	8	0.73	0.34-1.57	>275-1,323	6	0.62	0.26-1.46
>1,519	6	0.64	0.27-1.54	>1,323	8	0.97	0.45-2.11
<i>P</i> _{trend} ^c		0.13		<i>P</i> _{trend} ^c		0.74	
Leukemia							
0	119	1.00	REF	0	122	1.00	REF
>0-310	7	1.00	0.44-2.27	>0-275	7	1.19	0.53-2.70
>310-1,519	8	0.87	0.39-1.94	>275-1,323	5	0.63	0.24-1.65
>1,519	5	0.60	0.22-1.60	>1,323	5	0.71	0.27-1.87
<i>P</i> _{trend} ^c		0.30		<i>P</i> _{trend} ^c		0.44	
Oral cavity cancers							
0	88	1.00	REF	0	93	1.00	REF
>0-765	11	1.62	0.78-3.35	>0-661.5	6	0.96	0.39-2.37
>765	8	1.27	0.54-2.99	>661.5	8	1.33	0.57-3.09
<i>P</i> _{trend} ^c		0.79		<i>P</i> _{trend} ^c		0.49	
Colon cancer							
0	285	1.00	REF	0	299	1.00	REF
>0-310	27	1.57	1.02-2.41	>0-275	18	1.17	0.71-1.93
>310-1,519	15	0.68	0.39-1.20	>275-1,323	16	0.79	0.46-1.37
>1,519-4,032	18	1.63	0.96-2.77	>1,323-3,564	13	1.28	0.71-2.33
>4,032	7	0.81	0.37-1.79	>3,564	6	0.76	0.33-1.76
<i>P</i> _{trend} ^c		0.77		<i>P</i> _{trend} ^c		0.67	
Rectal cancer							
0	137	1.00	REF	0	142	1.00	REF
>0-310	10	1.21	0.61-2.40	>0-275	8	1.14	0.54-2.41
>310-1,519	7	0.69	0.30-1.56	>275-1,323	5	0.56	0.22-1.44
>1,519-4,032	6	1.22	0.51-2.95	>1,323-3,564	6	1.43	0.60-3.44
>4,032	5	1.38	0.53-3.63	>3,564	4	1.29	0.45-3.70

Intensity-weighted lifetime days	No. of cases	RR ^a	95% CI ^a	Intensity-weighted lifetime days, 15-year lag ^b	No. of cases	RR ^a	95% CI ^a
P_{trend}^c		0.48		P_{trend}^c		0.52	
Lung cancer							
0	345	1.00	REF	0	357	1.00	REF
>0–310	27	0.78	0.52–1.18	>0–275	28	0.94	0.63–1.41
>310–1,519	35	0.74	0.51–1.09	>275–1,323	27	0.67	0.44–1.01
>1,519–4,032	17	0.70	0.42–1.18	>1,323–3,564	13	0.64	0.36–1.13
>4,032	19	0.90	0.55–1.49	>3,564	17	0.94	0.55–1.58
P_{trend}^c		0.76		P_{trend}^c		0.65	
Bladder cancer							
0	174	1.00	REF	0	177	1.00	REF
>0–310	11	1.03	0.54–1.98	>0–275	11	1.25	0.65–2.39
>310–1,519	11	0.80	0.41–1.56	>275–1,323	10	0.86	0.43–1.73
>1,519	12	0.96	0.49–1.87	>1,323	10	0.97	0.48–1.96
P_{trend}^c		0.91		P_{trend}^c		0.85	
Kidney cancer							
0	121	1.00	REF	0	126	1.00	REF
>0–310	9	1.16	0.56–2.42	>0–275	6	0.90	0.38–2.13
>310–1,519	9	0.86	0.40–1.83	>275–1,323	7	0.77	0.34–1.76
>1,519	7	0.78	0.33–1.82	>1,323	7	0.89	0.38–2.07
P_{trend}^c		0.51		P_{trend}^c		0.81	
Melanoma							
0	161	1.00	REF	0	164	1.00	REF
>0–310	6	0.49	0.21–1.14	>0–275	5	0.53	0.21–1.33
>310–1,519	16	1.06	0.59–1.91	>275–1,323	14	1.20	0.65–2.22
>1,519	5	0.36	0.14–0.94	>1,323	5	0.47	0.18–1.22
P_{trend}^c		0.06		P_{trend}^c		0.17	

Abbreviations: CI, confidence interval; RR, rate ratio

^a Adjusted for age, gender, race, state of residence, applicator type, enrollment year, cigarette smoking status, alcohol consumption, education, family history of cancer (specific type where available), and ever/never categorizations of the five pesticides most highly correlated with methyl bromide: metalaxyl, ethylene dibromide, carbarth, aldicarb, and maneb/mancozeb

h Intensity-weighted lifetime days of methyl bromide application, discounting the most recent 15 years of exposure

c P -value for trend in cancer risk with increasing methyl bromide use

d Restricted to males

Methyl bromide use and cancer risk by family history of the specific cancer among pesticide applicators in the Agricultural Health Study, with follow-up from 1993–2007

Table 3

Cancer site	Exposure ^b	Among participants with a family history ^d			Among participants without a family history ^d			$P_{\text{interact}}^{d,e}$
		No. of cases ^c	RR ^d	95% CI ^d	No. of cases ^c	RR ^d	95% CI ^d	
Prostate ^f	Never	245	1.00	REF	1,167	1.00	REF	
	Ever	50	1.46	0.97–2.20	195	0.91	0.75–1.10	0.05
	T1	18	1.67	0.98–2.84	52	0.81	0.60–1.08	
	T2	15	1.28	0.71–2.30	76	0.97	0.75–1.26	
	T3	17	1.42	0.78–2.59	67	0.94	0.71–1.24	0.19
	P_{trend}^g		0.43			0.84		
Lung	Never	33	1.00	REF	269	1.00	REF	
	Ever	9	0.48	0.19–1.22	74	0.80	0.59–1.10	0.44
Colon	Never	33	1.00	REF	223	1.00	REF	
	Ever	3	1.09	0.25–4.70	51	1.15	0.78–1.70	0.19
Lymphohematopoietic	Never	23	1.00	REF	311	1.00	REF	
	Ever	3	1.61	0.34–7.58	53	0.96	0.66–1.38	0.67

Abbreviations: CI, 95% confidence interval; RR, rate ratio; T1–3, tertiles 1–3

^aFamily history of the specific cancer in a first-degree relative

^bTertiles defined based on intensity-weighted lifetime days of methyl bromide application among exposed cancer cases (all cancers combined), with cuts at 310 and 1,519 intensity-weighted days

^cCase counts do not sum to counts in Table 2 because of missing data for family history

^dAdjusted for age, gender, race, state of residence, applicator type, enrollment year, cigarette smoking status, alcohol consumption, education, and ever/never categorizations of the five pesticides most highly correlated with methyl bromide: metalaxyl, ethylene dibromide, carbarth, aldicarb, and maneb/mancozeb

^e P -value for interaction from the likelihood ratio test (LRT)

^fRestricted to males

^g P -value for trend in prostate cancer risk with increasing methyl bromide use