UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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**OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION**

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<u>MEMORANDUM</u>

Date: November 19, 2018

SUBJECT: **Methyl Bromide**: Tier I Update Review of Human Incidents and Epidemiology
for Draft Risk Assessment

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Decision No.: 545033	**Registration No.:** NA
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FROM: Elizabeth Evans, Environmental Protection Specialist
Erin Jones, Epidemiologist
Shanna Recore, Industrial Hygienist
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

THROUGH: David J. Miller, Acting Branch Chief
Toxicology and Epidemiology Branch
Health Effects Division (7509P)

TO: William Donovan, Risk Assessor
Risk Assessment Branch VII
Health Effects Division (7509P)
        and
Matthew Manupella, Chemical Review Manager
Risk Management & Implementation Branch 2
Pesticide Re-evaluation Division (7508P)

Summary and Conclusions

Methyl Bromide incidents were previously reviewed in 2013 (D411151, E. Evans and S. Recore, 5/22/13). At that time, the final phase of new soil fumigation safety mitigations had just been implemented[1] and it was too soon to review incidents for post-mitigation impact; thus, the 2013 memorandum described the methyl bromide incidents that occurred prior to the final mitigation implementation date. This earlier 2013 memo reported on 13 incidents from Main IDS and four incidents in Aggregate IDS, from January 1, 2008 to February 19, 2013. A query of SENSOR-Pesticides from 1998-2009 identified 119 case reports involving methyl bromide. The present Tier I Update includes a review of post-mitigation incidents.

In the current five-year IDS analysis, from January 1, 2013, to September 14, 2018, there were seven incidents in Main IDS that involved the active ingredient methyl bromide. One incident was a death involving an equipment failure that released methyl bromide resulting in the death of a worker. Two of the incidents were classified as major severity and four of the incidents were classified as moderate severity. In Aggregate IDS, four minor severity incidents were reported. In SENSOR-Pesticides from 2010-2015, 34 cases involving methyl bromide were identified.

A review of the year-by-year incidents over time in IDS shows that there were very few methyl bromide incidents reported both before and after- (the 2012) mitigation; however, there appears to be a slight decrease in the number methyl bromide incidents reported in SENSOR-Pesticides since the 2012 mitigation was implemented. While there were still some severe incidents and one fatality reported involving methyl bromide, the frequency of methyl bromide incidents reported to both the IDS and SENSOR datasets has remained low over time.

Additionally, the 2013 methyl bromide incident/epidemiology memo included a summary of methyl bromide epidemiology findings from the Agricultural Health Study (AHS) and a few studies outside of AHS where methyl bromide use is more frequent. The AHS is a federally-funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. The AHS participant cohort includes more than 89,000 licensed commercial and private pesticide applicators and their spouses from Iowa and North Carolina. Enrollment occurred from 1993 – 1997 and data collection is ongoing. The epidemiological findings from published AHS studies that report adverse health effects due to methyl bromide exposure and the three non-AHS studies mentioned in the 2013 memo are summarized in detail below. Overall, we considered the epidemiological evidence reviewed to be insufficient to conclude that a clear associative or causal relationship exists between methyl bromide exposure and the carcinogenic and non-carcinogenic health outcomes assessed in the studies reported here.

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[1] On December 1, 2012 the final phase EPA-required new safety measures for soil fumigant pesticides (chloropicrin, dazomet, metam sodium/potassium, and methyl bromide) went into effect. These safety measures are required to increase protections for agricultural workers and bystanders. Details on mitigation requirements and implementation can be found at: https://www.epa.gov/soil-fumigants/implementing-safety-measures.

I. ACTION REQUESTED

Methyl bromide is being considered under the FQPA-mandated Registration Review program established to review, on a 15-year cycle, pesticides for which a Re-registration Eligibility Decision has been made. HED's RAB VII has requested that TEB conduct a Tier I Update review summary of recent incident data from IDS and SENSOR as per standard protocol under the Agency's Registration Review Program. One component of the Agency's Registration Review Program is consideration of human incident data. In conjunction with a human health risk assessment based on other data sources, such human incident data can assist the Agency in better defining and characterizing the risk of pesticides/pesticide products.

It is important to remember that reports of adverse health effects allegedly due to a specific pesticide exposure (*i.e.*, an "incident") are largely self-reported and therefore neither exposure to a pesticide or reported symptom (or the connection between the two) is validated or otherwise confirmed. Typically, causation cannot be determined based on incident data, and such data should be interpreted with caution. Incident information provides an important source of feedback to the Agency: incidents of severe outcome, or a suggested pattern or trend among less severe incidents, can signal the Agency to further investigate a chemical or product.

Epidemiology studies can also be useful and relate the risk of disease, *e.g.*, cancer, and exposure to an agent such as a pesticide product in the general population or specific sub-groups like pesticide applicators.

II. BACKGROUND

Methyl bromide is a broad-spectrum fumigant chemical that can be used as an acaricide, antimicrobial, fungicide, herbicide, insecticide, nematicide, and vertebrate control agent. Methyl bromide's most prevalent use pattern is as a soil fumigant.[2] It is commonly formulated as pressurized gas applied as a soil fumigant via soil injection or deep drip irrigation. Methyl bromide can be used post-harvest via injection into an enclosure chamber, structure, or under a tarp. It is registered for use on the soils of all vegetable, fruit and nut crops, and for structural fumigation, post-harvest treatment of commodities (e.g. dates, figs, raisins, walnuts), and non-food uses (logs for export).

The 2006 TRED/RED found inhalation risks of concern for occupational handlers involved in methyl bromide applications and tarp perforation (e.g., cutting, punching, slicing, or poking the tarp) or removal activities. Risks are also of concern for workers who may re-enter treated areas shortly after fumigation or tarp perforation has been completed. Monitoring and modeling data indicate that there can be risks of concern associated with methyl bromide use at a broad range of distances from treated fields, depending on application method, emission control methods employed, application rate, and size of the area treated.[3]

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[2] Methyl Bromide factsheet: http://www.epa.gov/oppsrrd1/REDs/factsheets/methylbromide-fs.pdf
[3] Ibid.

In 2012, the EPA required additional new safety measures for all soil fumigant pesticides (chloropicrin, dazomet, metam sodium/potassium/MITC and methyl bromide) and these went into effect on December 1, 2012. These new safety requirements were implemented to increase protection for agricultural workers and bystanders. These safety measures included rate reductions, use site limitations, applicator training, and buffer zones around all treated fields. As part of this incent report, HED considered pre- and post-mitigation incidents to better illustrate, distinguish, and characterize incidents that occurred prior these mitigation actions and those that occurred after these mitigation actions. For more information on the new soil fumigant safety requirements visit: https://www.epa.gov/soil-fumigants/implementing-safety-measures.

For this evaluation, both the OPP Incident Data System (IDS) and the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) Sentinel Event Notification System for Occupational Risk-Pesticides (SENSOR) databases were consulted for pesticide incident data on the active ingredient Methyl bromide (PC Code: 053201). The purpose of the database search is to identify potential patterns in the frequency and severity of the health effects attributed to methyl bromide exposure.

In addition, findings from the AHS were reviewed. The Agricultural Health Study (AHS) is a high quality, prospective epidemiology study evaluating the link between pesticide use and various health outcomes including cancer.

III.   RESULTS/DISCUSSION

   a. IDS (Incident Data System)

OPP's IDS includes reports of alleged human health incidents from various sources, including mandatory Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) Section 6(a)(2) reports from registrants, other federal and state health and environmental agencies, and individual consumers. Since 1992, OPP has compiled these reports in IDS. IDS contains reports from across the U.S. and most incidents have all relevant product information recorded. Reports submitted to the IDS represent anecdotal reports or allegations only, unless otherwise stated in the report.

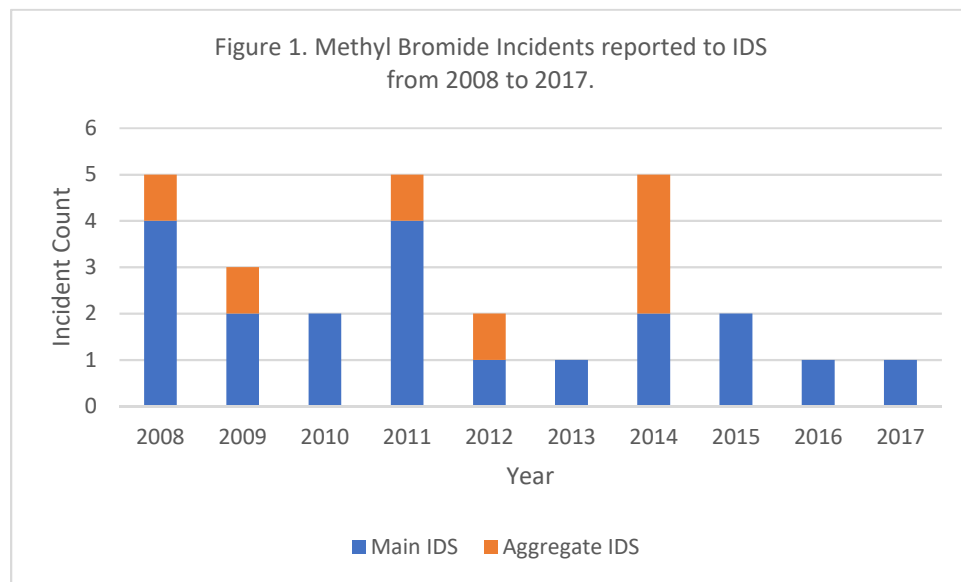IDS records incidents in one of two modules: Main IDS and Aggregate IDS:

o   Main IDS contains incidents resulting in higher severity outcomes and provides more detail with regard to case specifics. This system stores incident data for death, major and moderate incidents, and it includes information about the location, date and nature of the incident. Main IDS incidents involving only one active ingredient (as opposed to pesticide products with multiple active ingredients) are considered to provide more certain information about the potential effects of exposure from the pesticide.

o   Aggregate IDS contains incidents resulting in less severe human incidents (minor, unknown, or no effects outcomes). These are reported by registrants only as counts in what are aggregate summaries.

For the Main IDS for the period from January 1, 2013 to September 14, 2018, there were seven incidents reported that involved the active ingredient methyl bromide. Of these seven incidents, five incidents involved the single active ingredient methyl bromide (only) and two incidents involved methyl bromide and chloropicrin. Of the seven reported incidents, there was one fatality, two incidents were classified as major severity, and four incidents were classified as moderate severity.

Six of these incidents occurred in an occupational setting and two of these occupational incidents involved multiple people. The fatality occurred in Illinois in 2017. This was due to an equipment failure that released methyl bromide resulting in the death of a worker. The non-occupational incident occurred in 2015 and involved a family of four who were poisoned by exposure to methyl bromide while vacationing in the Virgin Islands. They experienced seizures and inability to breathe. All seven incident narratives are available in Appendix A.

For Aggregate IDS for the period from January 1, 2013 to September 14, 2018, there were three incidents reported involving methyl bromide. These incidents were classified as minor severity.

The methyl bromide incident trend from 2008 to 2017 was reviewed. In general, there were very few methyl bromide incidents reported to IDS (figure 1). The frequency of methyl bromide incidents remains low over time, varying between one and five per year over this period.

Figure 1. Methyl Bromide Incidents reported to IDS from 2008 to 2017.

b. SENSOR-Pesticides

The Center for Disease Control's National Institute for Occupational Safety and Health (CDC/NIOSH) manages a pesticide surveillance program and database entitled the Sentinel Event Notification System for Occupational Risk (SENSOR)-Pesticides.[4] All cases must report

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[4] SENSOR-Pesticides webpage: http://www.cdc.gov/niosh/topics/pesticides/overview.html.

at least two adverse health effects. Evidence for each case is evaluated for its causal relationship between exposure and illness based on the NIOSH case classification index.[5] Using standardized protocol and case definitions, SENSOR-Pesticides state coordinators, operating out of the state's department of health, receive state pesticide incident reports from local sources, then follow up with case sources to get incident scenario to obtain medical records and verify exposure scenario information.[6] This database includes pesticide illness case reports from multiple states from 1998-2015.[7]

Tier I Update Review of SENSOR-Pesticides Data (2010-2015)

When methyl bromide incidents were previously reviewed in 2013 (D411151, E. Evans and S. Recore, 5/22/13), SENSOR-Pesticides data from 1998-2009 was analyzed. For this Tier I Update, a query of SENSOR-Pesticides from 2010-2015 was conducted and identified 34 cases involving methyl bromide. One case was high in severity, nine cases were moderate in severity, and 24 cases were low in severity.[8] All 34 cases were work-related exposures. Inhalation was the primary exposure route among cases (n=26). Of the 34 cases, 20 were agricultural workers exposed while conducting routine fieldwork and were not involved in pesticide application.

The single high severity case was a fieldworker who was harvesting broccoli and got sick after a tarp in the adjacent field ruptured and caused the off-target movement of methyl bromide. The tarped soil application had taken place the day before this exposure event. The high severity case went to the hospital with burning, teary and painful eyes, dizziness, sore throat, shortness of breath, coughing, headache, chest pain, chills, fever and weakness. He was diagnosed with pneumonia, fever, chills, tachycardia, and dehydration. This high severity case was one of six workers harvesting broccoli and who were made ill from this event (one case was moderate in severity and four cases were low severity.

Occupational activities conducted by the 34 methyl bromide cases:
- 20 cases were agricultural workers conducting routine fieldwork activities,
- 7 cases were laborers who handle shipping boxes, crates and imported products,
- 4 cases were agricultural inspectors made ill while conducting fumigation inspections,
- 1 case was driver with pesticide manufacturing facility; and
- 2 cases worked in non-ag businesses located adjacent to farms and were exposed to off target movement from a nearby application.

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[5] https://www.cdc.gov/niosh/topics/pesticides/pdfs/casedef.pdf
[6] https://www.cdc.gov/niosh/topics/pesticides/pdfs/pest-sevindexv6.pdf
[7] Currently participating states are: California, Florida, Illinois, Louisiana, Michigan, Nebraska, New Mexico, North Carolina, Oregon, Texas and Washington. The participating states for a given year vary depending on state and federal funding for pesticide surveillance.
[8]

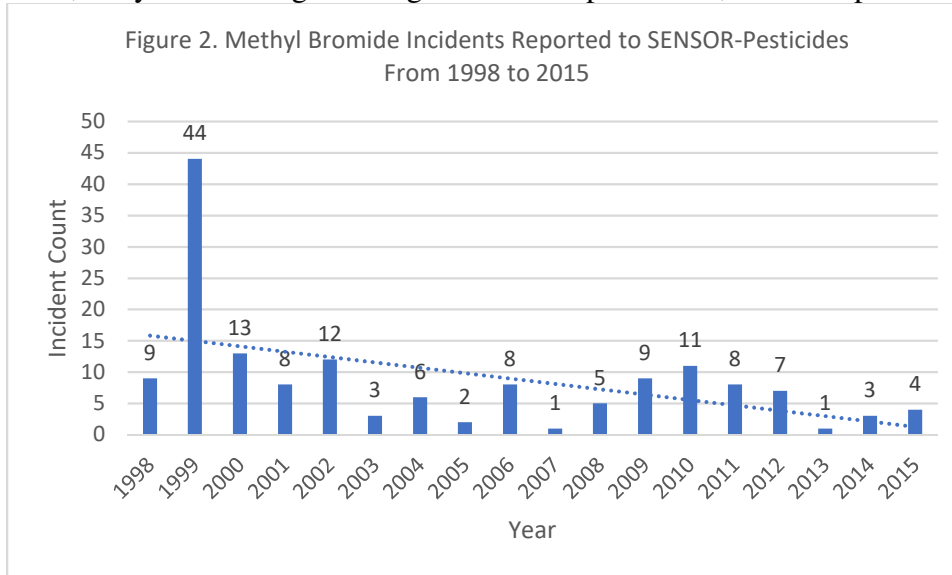| SENSOR-Pesticides Severity Index		
High	Life threatening, requires treatment	>5 days lost work/time
Moderate	Involves systemic effects, usually requires treatment	3-5 days lost work/time
Minor	Must report two or more symptoms; typically resolve without treatment	<3 days lost work/time

<u>Fumigation Tarps</u>
Eleven of the 34 methyl bromide cases involved fumigation tarps, and typically involved tarp rip/tears and tarp handling activities. Six of these were the cases involved in the tarp rupture event, including the high severity case, as described above. Four of the 11 cases were fieldworkers conducting tarp removal/disposal work, and one case was an agricultural inspector who was conducting a fumigation inspection; he noticed a hole in the tarping and subsequently became symptomatic.

<u>Health Effects</u>
Symptoms most frequently reported among cases included: eye pain/irritation and conjunctivitis, headache, nausea, dizziness, and upper respiratory pain/irritation.

The methyl bromide incidents reported to SENSOR-Pesticides appear to have decreased overtime from 1998 to 2015 (Figure 2). Incidents declined from seven reported incidents in 2012, the year of fumigant mitigation was implemented, to four reported incidents in 2015.

Figure 2. Methyl Bromide Incidents Reported to SENSOR-Pesticides From 1998 to 2015

Incident Conclusion

In the current IDS analysis from January 1, 2013, to September 14, 2018, there were seven incidents in Main IDS that involved the active ingredient methyl bromide. One incident involved an equipment failure that released methyl bromide resulting in the death of a worker. Two of the incidents were classified as major severity and four of the incidents were classified as moderate severity. These cases are described in Appendix A. In Aggregate IDS, four minor severity incidents were reported. In SENSOR-Pesticides from 2010-2015, 34 cases involving methyl bromide were identified. Thirty two percent of methyl bromide cases reported to SENSOR-Pesticides (2010-2015) involved exposure from tarp rip/tears or tarp handling activities.

A review of the year-by-year incidents over time in IDS shows that there were very few methyl bromide incidents reported both pre and post- (2012) mitigation; however, there appears to be a

slight decrease in the number methyl bromide incidents reported SENSOR-Pesticides since the 2012 mitigation was implemented. While there were still some severe incidents and one fatality reported involving methyl bromide, the frequency of methyl bromide incidents reported to both datasets has remained low over time.

c. Agricultural Health Study (AHS)

Methyl bromide is a pesticide investigated within the Agricultural Health Study (AHS). The AHS is a federally funded study that evaluates associations between pesticide exposures and cancer and other health outcomes and represents a collaborative effort between the US National Cancer Institute (NCI), the National Institute of Environmental Health Sciences (NIEHS), CDC's National Institute of Occupational Safety and Health (NIOSH), and the US EPA. The AHS participant cohort includes more than 89,000 licensed commercial and private pesticide applicators and their spouses from Iowa and North Carolina. Enrollment occurred from 1993 – 1997, and data collection is ongoing. The AHS maintains a list of publications resulting from AHS studies.[9]

In developing this Tier I Review Update, EPA reviewed the AHS publications listed on the AHS publication website as was done for the 2013 EPA Review of Human Incidents document. As of November 2018, 41 AHS publications that investigated associations between adverse health outcomes relative to methyl bromide reported estimates of effects. These studies are summarized below under the section headings "Carcinogenic Effects" and "Non-Carcinogenic Effects"[10], as well as in a summary table (see Appendix B). In addition to the review of AHS findings, the EPA evaluated three additional studies on other study populations because methyl bromide is less commonly used by AHS study participants. These studies were previously identified in EPA's 2013 scoping assessment and summarized in this review.[11]

Carcinogenic Effects

__All Cancers__

- Barry et al. (2012) evaluated the association between methyl bromide use and all cancers (combined) in addition to assessing several specific cancers individually using data from the Agricultural Health Study (AHS), a prospective cohort study of pesticide applicators in Iowa and North Carolina. Pesticide applicators in the AHS who reported a cancer diagnosis prior to enrollment (except for non-melanoma skin cancers), those lost to follow-up, and those missing data for methyl bromide exposure were excluded. Eligible cases included AHS study participants who were diagnosed with cancer after enrollment (1993 – 1997) through December 31, 2007. Cancer diagnosis were ascertained using

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[9] Agricultural Health Study: Publications https://aghealth.nih.gov/news/publications.html

[10] In evaluating and reporting on the AHS studies, for odds ratios (ORs), risk ratios (RRs), and hazard ratios (HRs), the confidence interval (CI) acted as a proxy for significance testing, with CIs that do not contain the null value (OR / RR / HR = 1.00) considered significant.

[11] Environmental Protection Agency (2013). Methyl Bromide: Human Health Assessment Scoping Document in Support of Registration Review. September 13, 2013. https://www.regulations.gov/contentStreamer?documentId=EPA-HQ-OPP-2013-0269-0004

state cancer registries and vital status was ascertained using state death registries and the National Death Index. Pesticide exposure was assessed via two self-administered questionnaires, one administered during study enrollment (1993 – 1997) and a second follow-up telephone questionnaire administered five years after enrollment (1999-2005) for which a 63% response rate was obtained. Authors used the following assumptions to impute methyl bromide use data for applicators missing methyl bromide use information on the follow-up questionnaire: 1) if applicators reported no use of methyl bromide prior to enrollment and did not provide information at follow-up, authors assumed they never used methyl bromide; 2) if applicators reported use of methyl bromide prior to enrollment and did not provide methyl bromide use on the follow-up survey, authors assigned methyl bromide exposure based on information reported at enrollment. Investigators used questionnaire data and imputation results to generate cumulative lifetime days of application, intensity-weighed lifetime days of use, and intensity-weighed lifetime days of use with a 15 year lag (to discount the most recent 15 years of exposure as many cancers have a long latency).[12] Exposure days were then categorized into tertiles based on distribution among the exposed cancer cases (all cases combined) with the highest tertile further divided at the median into a total of five categories (fewer categories were used for rarer cancers) and are detailed below.[13] Poisson regression was used to calculate 95% confidence intervals (CIs) and rate ratios (RR) for methyl bromide relative to all cancers (combined) and individual cancers, adjusting for age, gender, race, state, applicator type, enrollment year, cigarette smoking status, alcohol consumption, education, family history of cancer, and ever/never use of top five pesticides most highly correlated with methyl bromide exposure (metalaxyl, ethylene dibromide, carbaryl, aldicarb, and maneb/mancozeb). Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 786 were exposed cancer cases (combined). No evidence of a significant positive association was reported for all cancers and methyl bromide, with the no exposure group as the referent for any exposure category for either intensity-weighted lifetime days of exposure ($0.84 \leq RR \leq 1.08$, all CIs encompassed the null value of 1 for all exposure categories, with n = 129 – 264 cases, p-trend 0.96) or the intensity-weighted lifetime days of exposure with 15-year lag ($0.82 \leq RR \leq 1.07$, all CIs encompassed the null value of 1 for all exposure categories, with n = 110 – 223 cases, p-trend 0.86).

Bladder Cancer

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[12] Cumulative lifetime days of use is the product of years of use and the number of days used per year. Intensity-weighted lifetime days of use is defined as the product of exposure intensity (based on mixing status, application method, equipment repair, and use of personal protective equipment) and lifetime days of use.

[13] For intensity-weighted lifetime days of exposure, the following tertiles of exposure within this study were: for all cancers, prostate, lymphohematopoietic, colon, rectum, and lung cancers five categories: 0, >0 – 310, >310 – 1,519, >1,519– 4,032, and >4,032 days; four categories for NHL, leukemia, bladder, kidney, and melanoma cancers: 0, >0 – 310, >310 – 1,519, >1,519; and three categories for stomach cancer and oral cavity cancers: 0-765, >765. For intensity-weighted lifetime days of exposure with 15-year lag, the following tertiles of exposure within this study were: five categories for all cancers, prostate, lymphohematopoietic, colon, rectum, and lung cancers: 0, >0 – 275, >275 – 1,323, >1,323– 3,564, and >3,564 days; four categories for NHL, leukemia, bladder, kidney, and melanoma cancers: 0, >0 – 275, >275 – 1,323, >1,323; and two categories for stomach and oral cavity cancers: 0-661.5, >661.5.

The association between methyl bromide exposure and bladder cancer was evaluated in two AHS studies (Barry et al., 2012; Koutros et al., 2016) described below.

- Barry et al. (2012) evaluated the association between methyl bromide use and bladder cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 34 were exposed bladder cancer cases. No evidence of a significant positive association was observed for bladder cancer at any exposure level for either intensity-weighted lifetime days of exposure ($0.80 \leq RR \leq 1.03$; all CIs encompassed the null value of 1 for all exposure categories, with 11 – 12 cases per exposure category, with a p-trend = 0.91) or the intensity-weighted lifetime days of exposure with 15-year lag ($0.86 \leq RR \leq 1.25$; all CIs encompassed the null value of 1 for all exposure categories, with 10 – 11 cases per exposure category, with a p-trend = 0.85).

- Koutros et al. (2016) used data from the Agricultural Health Study (AHS), a prospective cohort study of pesticide applicators in Iowa and North Carolina, to investigate the association between bladder cancer incidence and pesticide exposure, including methyl bromide. The study population consisted of male pesticide applicators with incident bladder cancer cases identified through cancer registry files in Iowa and North Carolina. Pesticide exposure was assessed via two self-administered questionnaires, one administered during study enrollment (1993 – 1997) and a second follow-up questionnaire administered five years after enrollment (1999-2005) for which a 63% response rate was obtained. For the remaining 37% of applicators, a data-driven multiple imputation procedure was used to ascertain use of specific pesticides at follow-up. Investigators used questionnaire data and imputation results to generate cumulative lifetime days of use and intensity-weighed lifetime days of use.[14] Poisson regression analysis was used to calculate RRs and 95% CIs controlling for age, race, state of residence, pack-years of cigarettes, and pipe smoking. Among the study population (n = 54,344), 321 incident bladder cancer cases were reported from study enrollment through follow-up in 2010 (in North Carolina) and 2011 (in Iowa), and 48 of the cases reported exposure to methyl bromide. The investigators observed no evidence of a positive association between ever/never use of methyl bromide and bladder cancer (RR = 0.86, 95% CI: 0.60, 1.23). A further analysis stratified the cumulative intensity-weighted lifetime days of pesticide exposures, including methyl bromide exposure overall, and by smoking status (never, former and current) to elucidate any confounding with smoking, a known cause of bladder cancer. For methyl bromide, no evidence of a significant positive association was observed in any exposure tertile for overall cumulative exposure or for cumulative exposure stratified by never, former, or current smoking status, relative to the referent group with no methyl bromide exposure ($0.29 \leq RR \leq 1.29$; all CIs encompassed the null value of 1; with 3 – 16 cases per tertile, and p-trends: 0.99, 0.81, 0.60, and 0.47). There was no evidence of an effect modification by smoking on the

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[14] Cumulative lifetime days of use is the product of years of use and the number of days used per year. Intensity-weighted lifetime days of use is defined as the product of exposure intensity (based on mixing status, application method, equipment repair, and use of personal protective equipment) and lifetime days of use.

relationship between cumulative intensity-weighted days of methyl bromide and bladder cancer (p-interaction = 0.55).

Lung Cancer

The association between methyl bromide exposure and lung cancer was evaluated in two AHS studies (Barry et al., 2012; Bonner et al., 2017) described below.

- Barry et al. (2012) evaluated the association between methyl bromide use and lung cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 98 were exposed lung cancer cases. No evidence of a positive association was observed for lung cancer at any exposure level for either intensity-weighted lifetime days of exposure (0.70 $\leq$ RR $\leq$ 0.90; all CIs encompassed the null value of 1 for all exposure categories, with 17 – 35 cases per exposure category, with a p-trend = 0.76) or the intensity-weighted lifetime days of exposure with 15-year lag (0.64 $\leq$ RR $\leq$ 0.94; all CIs encompassed the null value of 1 for all exposure categories, with 13 – 28 cases per exposure category, with a p-trend = 0.65).

- Bonner et al. (2017) investigated the association between lung cancer and exposure to pesticides including methyl bromide, using data from the AHS prospective cohort of pesticide applicators living in Iowa and North Carolina. Incident lung cancer cases were identified at study enrollment (1993-1997) through December 2010 (North Carolina) and December 2011 (Iowa), using cancer registry files in Iowa and North Carolina. Pesticide exposure was assessed through self-administered questionnaires, one completed during study enrollment and a second more detailed questionnaire completed at home shortly afterwards (1993 – 1997). Investigators used questionnaire data to determine ever/never use of individual pesticides and calculate cumulative exposure scores. For methyl bromide, quartiles of 20 – 44 exposed cases each were constructed based on lifetime days of exposure, and quartiles of 26 – 31 exposed cases each were constructed based on intensity-weighted lifetime-days of exposure. A Cox proportional hazards analysis was used to calculate Hazard Ratios (HR) and 95% CIs, controlling for smoking (pack years), gender, total lifetime pesticide use, and age. Of the 57,310 study participants, 654 incident lung cancer cases were identified. No evidence of a significant positive association was reported at any exposure level for either lifetime days of exposure or for intensity-weighted lifetime-days of exposure for methyl bromide and lung cancer in applicators with non-exposed as the referent (0.89 $\leq$ HR $\leq$ 1.14; all 95% CIs encompassed the null value of 1; p-trends = 0.432, 0.706).

Breast Cancer

- Engel et al. (2005) evaluated the association between breast cancer incidence among farmers' wives and specific pesticides including methyl bromide. Pesticide exposure was assessed based on self-reported questionnaires completed by AHS participants during

study enrollment (1993 – 1997). Breast cancer cases were identified using cancer registries in Iowa and North Carolina between enrollment through December 2000. Poisson regression was used to calculate 95% CIs and RRs for individual pesticides, and each analysis was adjusted for age, race, and state of residence. Of the 309 incident breast cancer cases identified within the cohort (n = 30,454) between study enrollment and December 31, 2000, a total of 7 (2.3%) women reported exposure to methyl bromide. Of the 30,145 controls (women not diagnosed with breast cancer) with complete data, a total of 350 (1.2%) women reported methyl bromide use. The authors reported no evidence of a significant positive association between breast cancer incidence and ever exposure to methyl bromide among farmers' wives (RR = 1.50; 95% CI: 0.70, 3.20). For husband's use among wives who never use pesticides, 21 (16%) cases and 1,921 (16.30%) noncases reported methyl bromide exposure, and no evidence of a positive association was observed (RR = 1.00: 95% CI: 0.60, 1.70). When stratified by state and adjusted for age and race, there was no evidence of a significant positive association observed for wife's pesticide use among all wives from North Carolina (RR = 1.4; 95% CI: 0.60, 3.20 with noncases 305, 6 cases) and no evidence of a positive association among husband's pesticide use among wives who never use pesticides from North Carolina (RR = 1.0; 95% CI: 0.60, 1.80 with noncases 1,814, 20 cases). The association between breast cancer incidence and ever exposure to methyl bromide in participants from Iowa could not be assessed in this study due to the small number of exposed cases (n < 3) in both categories: wife's pesticide use among all wives and among exposed cases and husband's pesticide use among wives who never used pesticides. When stratified by menopausal status at enrollment (premenopausal vs. postmenopausal) and adjusted for age, race, and state, there was no evidence of a significant positive association between breast cancer incidence and ever exposure to methyl bromide among farmers' wives who were premenopausal (RR = 1.9; 95% CI: 0.60, 6.10 with noncases 161, 3 cases) or postmenopausal at enrollment (RR = 1.4; 95% CI: 0.50, 3.80 with noncases 150, 4 cases). For husband's use among wives who never use pesticides stratified by menopausal status, no evidence of a positive association between husband's methyl bromide use and wife's risk of breast cancer was observed for either premenopausal (RR = 0.8; 95% CI: 0.30, 2.50 with noncases 718, 5 cases) or postmenopausal categories (RR = 1.0; 95% CI: 0.50, 1.90 with noncases 810, 14 cases).

Prostate Cancer

The association between methyl bromide exposure and prostate cancer was evaluated in five AHS studies (Alavanja et al., 2003; Koutros et al., 2011; Barry et al., 2011; Barry et al., 2012; Koutros et al., 2013) and two additional studies (Cockburn et al., 2011 and Mills and Yang, 2003) described below.

- Alavanja et al. (2003) evaluated the potential association between prostate cancer and exposure to pesticides including methyl bromide. Using data from the AHS, the study population consisted of male pesticide applicators living in Iowa and North Carolina, enrolled in the AHS prospective cohort. Incident prostate cancer cases were identified at study enrollment (1993-1997) through December 31, 1999, using cancer registry files in Iowa and North Carolina, and vital status was ascertained using state death records and

the National Death Index. Exposure was assessed through self-administered questionnaires, one completed during study enrollment and a second more detailed questionnaire completed at home shortly afterwards. Investigators used questionnaire data to determine ever/never use and to calculate cumulative exposure scores of individual pesticides. An unconditional logistic regression analysis was used to calculate odds ratios (OR) and 95% CIs to evaluate risks associated with exposure to methyl bromide and prostate cancer, controlling for family history of prostate cancer and age. Further analyses considered cumulative exposure (application days per year x total years of exposure x exposure intensity index) for pesticides including methyl bromide. Participants were assigned exposure scores and then were divided into tertiles with the upper tertile divided in half, and the upper half then divided in half again and resulted in the following five categories of exposure (with I being lowest exposure and V being highest exposure): I - lowest exposure : 0.10 - 33.3 percentile of use; II: 33.40 - 66.70 percentile of use; III - medium exposure: 66.80 - 83.30 percentile of use; IV: 83.40 - 91.60 percentile of use); and V - highest exposure: >91.60 percentile of use; with the no exposure category as the referent. Among the 55,332 participants in the study, 84 of the 566 prostate cancer cases reported exposure to methyl bromide. The study reported no evidence of a significant positive association between methyl bromide and prostate cancer based on ever/never use of methyl bromide (OR = 1.10; 95% CI: 0.77, 1.36). Further analyses that considered the association between cumulative exposure scores for methyl bromide and prostate cancer among pesticide applicators using the exposure categories previously described, demonstrated evidence of a statistically significant exposure-response relationship between increasing exposure to methyl bromide and prostate cancer among 67 exposed cases (lowest exposure I: OR = 1.01 (95% CI: 0.66, 1.56) with n = 23 cases; II: OR = 0.76 (95% CI: 0.47, 1.25) with n = 22 cases; III - medium exposure: OR = 0.70 (95% CI: 0.38, 1.28) with n = 11 cases; IV: OR = 2.73 (95% CI: 1.18, 6.33) with n = 6 cases; V - highest exposure: OR = 3.47 (95% CI: 1.37, 8.76) with n = 5 cases; p-trend = 0.004). Evidence of a strong association was observed in the highest exposure category and a moderately strong association was observed in the second highest category; however, no evidence of a significant positive association was observed in any of the three lower exposure categories for methyl bromide. In a further analysis conducted by the authors that considered state of residence of pesticide applicators, methyl bromide use and prostate cancer, methyl bromide use was also associated with a significantly increased risk of prostate cancer among private applicators in both states, with a linear trend p of 0.05 in North Carolina (ORs for previously defined categories = 1 (reference), 0.90, 0.80, 0.70, 2.80, and 3.80, confidence intervals were not provided) and a linear trend p of 0.04 in Iowa (ORs for previously defined exposure categories = 1 (reference), 1.70, 1.20, and 4.40; no cases in higher exposure categories, confidence intervals were not provided) and among commercial applicators in Iowa with a linear trend p = 0.01 (ORs for previously defined exposure categories = 1 (reference), 1.10, 3.10, 8.90, and 14; no cases in the highest exposure category, confidence intervals not provided). When frequency of use and lifetime application days were assessed across the same categories, significant exposure-response trends were observed for frequency of use, with p = 0.02 (ORs = 1 (reference), 0.93, 0.76, 1.31, 1.44, and 4.39, confidence intervals not provided), and lifetime application days, with p = 0.02 (ORs = 0.87, 0.78, 0.97, 2.09, and 2.63, confidence intervals not provided).

In an additional analysis conducted as part of this study that assessed the potential effect modification of a family history of prostate cancer on the association between methyl bromide and prostate cancer, Alavanja et al. (2003) included a cross-product term (family history × pesticide exposure) in the logistic model. No evidence of a significant positive association was observed between prostate cancer and methyl bromide exposure among those with a family history of prostate cancer (OR = 1.31, 95% CI: 0.75, 2.29, with 16 cases) or for those without a family history of prostate cancer (OR = 0.93, 95% CI: 0.70, 1.23, with 58 cases), and, no evidence of a significant interaction was observed for the interaction analysis of family history of prostate cancer on the relationship between exposure to methyl bromide and prostate cancer (interaction OR = 1.36, 95% CI: 0.73, 2.54, with 16 cases with a family history of prostate cancer and 58 cases with no history of prostate cancer, p-interaction = 0.34).

- Koutros et al. (2011) investigated the interaction between genetic variants, pesticide exposure including methyl bromide, and the risk of prostate cancer in a nested case-control study using data from the ongoing, prospective AHS. The study population consisted of male pesticide applicators living in Iowa and North Carolina, enrolled in the AHS cohort. The cases (n = 776) included men diagnosed with prostate cancer between 1993 and 2004 and state cancer registries confirmed the diagnoses. Controls (n = 1,444) included male pesticide applicators who reported no previous cancer diagnosis (exception for non-melanoma skin cancer) and were alive and not lost to follow-up at the time of case diagnosis. Controls were frequency-matched to the cases (2:1) via birthdate (+/- 1 year). Pesticide exposure was determined by two questionnaires completed at enrollment and a follow-up telephone interview five years later (1999 – 2003). Exposure was categorized by lifetime exposure days into non-exposed, low, and high exposure categories, based on the median cut-point determined from the distribution of lifetime exposure days of both the controls and cases. An unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures, and was adjusted for state, age, and family history of prostate cancer. The study reported no evidence of a significant positive association between methyl bromide exposure and prostate cancer in either the low or high exposure categories (low: OR = 0.88; 95% CI: 0.60, 1.28, with 52 cases and 108 controls; high: OR = 1.05; 95% CI: 0.71, 1.53, with 56 cases and 97 controls), and no evidence of an exposure-response relationship (p-trend = 0.799). A further analysis was conducted to examine potential interactions among pesticide exposures including methyl bromide, the risk of prostate cancer, and genes involved in various xenobiotic metabolizing enzyme pathways; however, this interaction analysis was not considered for this epidemiology review.

- Barry et al. (2011) investigated the association between pesticide exposures including methyl bromide and prostate cancer, and genetic variation among Base Excision Repair (BER) pathway genes. A nested case-control study was conducted using data from the ongoing, prospective AHS. The study population included white male pesticide applicators, living in Iowa or North Carolina, and eligible cases for the nested-case control study included AHS study participants who were diagnosed with prostate cancer between 1993 – 2004. Cases were ascertained through state cancer registries. Controls included white male applicators, with no previous cancer history (except non-melanoma

skin cancer), who were frequency-matched to the cases (2:1) by birth date (± 1 year). Pesticide exposure was assessed through two self-administered questionnaires at time of study enrollment, and exposure was classified via intensity-weighted lifetime exposure days and categorized into non-exposed, low, and high exposure groups. Unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticides including methyl bromide relative to prostate cancer risk, adjusting for state and age. Among the total cases (n = 776) and controls (n = 1,444), respectively, 637 cases and 1,215 controls reported no methyl bromide exposure. No evidence of a significant positive association was observed between methyl bromide exposure and prostate cancer among white male pesticide applicators in either the low or high exposure categories, relative to the non-exposed group (low: OR = 0.83; 95% CI: 0.56, 1.23, with 45 cases and 101 controls; high: OR = 1.15; 95% CI: 0.79, 1.68 with 61 cases and 98 controls) and no evidence of a significant exposure response trend (p-trend = 0.38). A further analysis was conducted to examine potential interactions among pesticide exposures including methyl bromide, the risk of prostate cancer, and genes involved in BER pathways; however, this interaction analysis was not considered for this epidemiology review.

- In a follow-up study to Alavanja et al. (2003), Barry et al. (2012) evaluated the association between methyl bromide use and prostate cancer, in addition to assessing all cancers (combined) and several individual cancers using data from a follow-up questionnaire administered five years after enrollment (1999-2005). See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 280 were exposed prostate cancer cases. For the analysis of intensity-weighted lifetime days of exposure to methyl bromide, no evidence of a positive association was reported for methyl bromide and prostate cancer at any exposure category, with the no exposure group as the referent (0.86 ≤ RR ≤ 0.99; CIs encompassed the null value of 1 for all exposure categories, with 44 – 108 cases per exposure category, with p-trend 0.90). For the analysis of intensity-weighted lifetime days of exposure with 15-year lag, no evidence of a significant positive association was observed at any exposure category (0.79 ≤ RR ≤ 1.01, all CIs encompassed the null value of 1 for all exposure categories, with n = 39 – 85 cases per exposure category, p-trend 0.81). Because a previous AHS analysis (Alavanja et al. 2003) demonstrated a positive association between methyl bromide and prostate cancer using follow-up data through 1999, and Barry et al. (2012) did not demonstrate a positive association among the 280 exposed cases when additional follow-up time through 2007 was taken into account, Barry et al. (2012) conducted a further analysis. The authors examined the effect modification of the association between high methyl bromide use (upper half of the highest tertile of intensity-weighted lifetime days compared with no methyl bromide use) and prostate cancer risk categories of calendar year of follow-up time among male pesticide applicators using a fitted trend on a log-linear scale. The study reported no significant variation in the RRs by calendar time (likelihood ratio test (LRT) p-interaction = 0.81), and no evidence of a significant positive association between prostate cancer and methyl bromide in the highest exposure category (compared with the non-exposed group with follow-up from 1993 – 1998 (RR = 1.52; 95% CI: 0.90, 2.59, with n = 18 cases) and the elevated yet insignificant risk diminished over time. In an additional analysis that compared methyl bromide ever/never use with risk of prostate cancer among pesticide applicators with a family history of prostate cancer to

those without a family history of prostate cancer using follow-up data from 1993 through 2007, a statistically significant interaction was observed (p-interaction = 0.05, LRT), however no evidence of a significant positive association was observed for ever use of methyl bromide and prostate cancer among participants with a family history of prostate cancer (RR = 1.46; 95% CI: 0.97, 2.20, with n = 50 cases) and no evidence of an association among participants without a family history of prostate cancer (RR = 0.91; 95% CI: 0.75, 1.10, with n = 195 cases). For a similar analysis where intensity-weighted lifetime days of methyl bromide use was divided into tertiles of use (cuts at 310 and 1,519 intensity-weighted days) to assess the effect of family history of prostate cancer on the association between prostate cancer and methyl bromide exposure (again using follow-up data from 1993 through 2007), no evidence of a significant positive association was reported for any exposure level of methyl bromide among participants with a family history of prostate cancer (1.28 $\leq$ RR $\leq$ 1.67; all 95% CIs encompassed the null value of 1; with 15 – 18 cases per exposure category p-trend = 0.43) and no evidence of a positive association was observed for prostate cancer and methyl bromide exposure among participants without a family history of prostate cancer (0.81$\leq$ RR $\leq$ 0.97; all 95% CIs encompassed the null value of 1; with 52 – 76 cases per exposure category; p-trend = 0.84) and the interaction was not significant (p-interaction = 0.19). The interaction with family history was significant for ever/never use of methyl bromide; however, the association did not persist with longer follow-up as demonstrated in the comparison of tertiles.

- In another follow-up study to Alavanja et al. (2003), Koutros et al. (2013) evaluated the potential association between prostate cancer -- total and aggressive[15] -- and exposure to pesticides including methyl bromide. Using data from the AHS, the study population consisted of male pesticide applicators living in Iowa and North Carolina, enrolled in the AHS prospective cohort. Incident prostate cancer cases were identified at study enrollment (1993-1997) through December 31, 2007 using cancer registry files in Iowa and North Carolina. Vital status was ascertained using state death records and the National Death Index. Controls included AHS study participants who had not been diagnosed with prostate cancer. Pesticide exposure was assessed through self-administered questionnaires, one completed during study enrollment, a second more detailed questionnaire completed at home shortly after enrollment, and a follow-up questionnaire administered 5 years after enrollment completed by 36,342 (63%) of original participants. For the 20,968 (37%) participants who did not complete a follow-up questionnaire, authors used a data-driven multiple imputation procedure that included logistic regression and stratified sampling to impute use of specific pesticides. Investigators used questionnaire data to determine ever/never use of individual pesticides and to calculate cumulative exposure scores. Cumulative exposure was assessed using lifetime days of pesticide use (years or pesticide use x number of days used per year) and intensity-weighted lifetime days of use (lifetime days of use x exposure intensity). Poisson regression was used to calculate RRs controlling for family history of prostate cancer, age, state, race, smoking, fruit servings, and leisure-time physical activity in

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[15] The study defined aggressive prostate cancer as "having 1 or more of the following tumor characteristics: distant stage, poorly differentiated grade, Gleason score of $\geq$ 7, or fatal prostate cancer (underlying cause, prostate cancer). Two alternative definitions of aggressive prostate cancer were also considered in analysis (using a Gleason score cutoff of $\geq$ 4 + 3 or a Gleason score of $\geq$ 8) in combination with other factors listed above (stage, fatal disease)." (Koutros et al. 2013)

winter. Among the study population (n = 54,412), 1,962 incident prostate cancer cases were reported, and 281 (14.3%) of the cases reported exposure to methyl bromide. Quartiles of exposed cases were constructed based on intensity-weighted lifetime-days of exposure for total prostate cancer (69 – 72 cases per quartile) and aggressive prostate cancer (29 – 30 cases/quartile), and the following exposure median for total prostate cancer was reported for each exposure quartile (units were not provided): Q1: 3.5, Q2: 15.5, Q3: 35.0, and Q4: 122.5. No evidence of a significant positive association was reported for *total* prostate cancer relative to methyl bromide exposure in any exposure quartile ($0.90 \leq RR \leq 0.94$; all CIs encompassed the null value of 1 for all exposure categories; with 69 – 72 cases per exposure category, p-trend = 0.66). And, similarly, no evidence of a positive association was reported for *aggressive* prostate cancer relative to methyl bromide exposure in any exposure quartile ($0.79 \leq RR \leq 1.17$; all CIs encompassed the null value of 1 in all exposure categories; with 29 – 30 cases per exposure category, p-trend = 0.78).

An additional analysis conducted by the authors compared risk of total prostate cancer and family history of prostate cancer and exposure to methyl bromide using the above exposure quartiles with cases 45 – 55 cases per exposure quartile for no family history of prostate cancer and 10 – 16 cases per exposure quartile for those with a family history of prostate cancer. Evidence of a moderately strong positive association was reported for methyl bromide exposure with family history of prostate cancer at the mid exposure level (>35 -122.5: RR = 2.00; 95% CI: 1.10, 3.67, with n = 13 cases) with non-exposed as the referent. No evidence of a significant positive association was observed for any other quartile in men with exposure to methyl bromide with or without a family history of prostate cancer ($0.81 \leq RR \leq 1.58$; all CIs encompassed the null value of 1; without family history of prostate cancer: p-trend = 0.97, and with family history of prostate cancer: p-trend= 0.79). There was no evidence of a statistically significant interaction (p-interaction = 0.10).

In addition to the review of AHS findings, the EPA considered two studies on other agricultural study populations (Cockburn et al., 2011; Mills and Yang et al., 2003) that evaluated the association between methyl bromide and prostate cancer, because methyl bromide is less commonly used by AHS study participants. These studies were previously identified in EPA's 2013 scoping assessment and are summarized in this review below.[11]

- Cockburn et al. (2011), investigated ambient pesticide exposure including methyl bromide and prostate cancer in a population-based case control study in the agriculturally intensive Central Valley of California (Tulare, Fresno, and Kern counties). Cases were identified from the California Cancer Registry and were diagnosed with histologically confirmed prostate cancer between August 2005 and July 2006, between 60 – 74 years of age, and were Latino/non-Latino whites. Controls were identified from Medicare lists in 2001 and from tax assessor mailings thereafter and were being recruited for a Parkinson's disease study in the same study area. Controls were recruited between 2004 – 2006, were ≥ 65 years of age, and did not report either Parkinson's disease or prostate cancer. Eligible cases and controls were currently residing primarily in the study area and had lived in California at least 5 years prior to enrollment. Past ambient pesticide exposures

occurring between 1974 – 1999 were derived from residential history, self-reported residential and occupational pesticide use, California Department Pesticide Regulation Pesticide Use Report data, and California's Public Land Survey land-use data. Potential pesticide exposure for an individual's residential time and place was determined by summing data on pesticide use within a 500-m buffer around the dwelling. Unconditional logistic regression was used to determine ORs and 95% CIs, adjusted for age, race/ethnicity, self-reported home pesticide use, and occupational pesticide exposure. Authors imputed missing exposure data by averaging the data from the non-missing years for the same individual (time-weighted average approach). Among the 173 cases and 162 controls, respectively, 87 cases and 70 controls reported exposure to methyl bromide. Evidence of a positive association between prostate cancer and residential proximity to agricultural fields treated with methyl bromide was observed (OR = 1.62; 95% CI: 1.02, 2.59) based on ever/never exposure for methyl bromide and California Pesticide Use Reports and address data for 1974-1999. When exposure was stratified into high and low exposure categories with no exposure as the referent, evidence of a positive association was reported for only the low level of exposure (OR 1.81; 95% CI: 1.03, 3.18), no evidence of a significant positive association was observed at the high level, and no evidence of a dose-response relationship (p-trend = 0.10) was observed. In an additional analysis that restricted the exposures to the diagnosis address of cases and recruitment address of controls, evidence of a strong association was observed for prostate cancer and residential proximity to agricultural fields treated with methyl bromide (OR = 3.60; 95% CI: 1.60, 8.20) based on ever/never exposure and when stratified by high and low exposure, evidence of an exposure-response was observed (low OR = 2.75, high OR = 4.01, p-difference = 0.0009, 95% CIs were not provided). This study did not perform actual measurements of methyl bromide, but rather relied on historical data regarding self-reported residence location (i.e., whether or not the residence was located within 500-m of a methyl bromide-treated field) and methyl bromide application data from the CA Pesticide Use Database.

- Mills and Yang et al. (2003) investigated the potential association between prostate cancer and pesticide exposures, including methyl bromide from farm work in a nested case-control study using data from a large, prospective cohort study of farmers who were part of the United Farm Workers of America (UFW). The study population consisted of Hispanic farm workers living in California, enrolled in the cohort. Incident cancer cases were identified by linking the UFW cohort to state cancer registry files between 1988 and 1999, and the controls, randomly selected from the remaining UFW cohort and age-matched (5:1) to the cases, were cancer free and were required to have lived at least through the year of diagnosis of their corresponding case. Pesticide exposure for the cases and controls was assessed using three different types of records/databases: UFW records to verify occupational history, grower's contracts to establish the crop/commodity the member was exposed to, and the California Department of Pesticide Regulation to determine specific pesticide usage. Conditional logistic regression was used to determine ORs and 95% CIs, controlling for age, sex, duration of union affiliation, and start date of first union affiliation. Among 222 prostate cancer cases and 1,110 age matched controls within a California farmworker population, Mills et al. (2003) reported no evidence of a significant positive association with exposure to methyl bromide (high vs. low level of

exposure) (OR high: 1.16; 95% CI: 0.77, 1.75, with n = 133 cases with high exposure, 89 cases with low exposure). And when methyl bromide exposure was further stratified by quartile of methyl bromide use, no evidence of a significant positive association between prostate cancer and methyl bromide use was observed (in any quartile), with the low exposure group as the referent ($1.17 \leq OR \leq 1.59$; CIs encompassed the null value of 1.00 for all exposure categories, with 32 – 64 cases per exposure category; p-trend = 0.25).

Stomach Cancer

The association between methyl bromide exposure and stomach cancer was evaluated in one AHS study (Barry et al., 2012) and an additional study (Mills and Yang, 2007) described below.

- Barry et al. (2012) evaluated the association between methyl bromide use and stomach cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.60%) reported any use of methyl bromide and of those with methyl bromide exposure, 15 were exposed stomach cancer cases. Evidence of a strong association and statistically significant trend was reported for stomach cancer and intensity-weighted lifetime days of exposure for high use with no exposure group as the referent (>765 days of use: RR = 3.13; 95% CI, 1.25, 7.80, with n = 10 cases) but no evidence of a significant positive association was reported for the low exposure category (>0 – 765 days of use: RR = 1.42; 95% CI: 0.51, 3.95, with n = 5 cases). Similarly, for intensity-weighted lifetime days of exposure with 15-year lag evidence of a strong association was observed for the high exposure category (RR = 3.33; 95% CI: 1.30, 8.51, with n = 9 cases) and no evidence of a significant positive association was noted for low exposure category (RR = 1.71; 95% CI: 0.61, 4.77, with n = 5 cases), with the no exposure group as the referent. For the 15 cases reporting stomach cancer and methyl bromide use, stomach cancer risk increased monotonically with increasing methyl bromide use for both intensity weighted lifetime days and intensity weighted lifetime days with 15-year lag, compared with no use (p-trend = 0.02, p-trend=0.02).

- In addition to the review of AHS findings, the EPA considered one study on another agricultural study population (Mills and Yang et al., 2007) that evaluated the association between methyl bromide and stomach cancer because methyl bromide is less commonly used by AHS study participants. This study was previously identified in EPA's 2013 scoping.[11] Here, the potential association between stomach cancer and pesticide exposures including methyl bromide from farm work was investigated. A nested case-control study was conducted using data from a large, prospective cohort study that included farmers who were part of the UFW, and the study population consisted of Hispanic farm workers living in California, enrolled in the cohort. Incident cancer cases were identified by linking the UFW cohort to state cancer registry files between 1988 and 2003, and the controls (no stomach cancer) from the cohort were frequency-matched to the cases via birthdate, gender, and ethnicity, respectively. All of the controls selected were then required to provide proof of residence in the state of California during the time of the corresponding case's diagnosis. Exposure for the cases and controls was assessed

using three different types of records/databases: (i) UFW records to verify occupational history; (ii) grower's contracts to establish the crop/commodity the member was exposed to; and (iii) the California Department of Pesticide Regulation to determine specific pesticide usage. To calculate ORs, exposures were initially dichotomized (ever/never use) based on pounds of use of each pesticide. Age-adjusted ORs and multivariable-adjusted ORs (and their corresponding 95% CIs) were then each calculated separately using the Mantel-Haenszel method and an unconditional logistic regression.[16] A total of 100 stomach cancer cases (22 females, 78 males) were reported, with 62 of the cases reporting exposure to methyl bromide. No evidence of a positive association between methyl bromide exposure and stomach cancer was observed (OR = 1.01; 95% CI: 0.59, 1.74) based on ever/never use. When the data was further stratified into quartiles[17] based on pounds of use of methyl bromide, with the no exposure group as the referent, no evidence of a significant positive association was observed in any exposure category ($0.56 \leq$ OR ≤ 1.33, CIs encompassed the null value of 1.00 for all exposure categories, with 12 – 27 cases per exposure category). No evidence of a positive association between stomach cancer and methyl bromide use was observed (in any quartile) in the age-adjusted analysis, with the *no* exposure group as the referent ($0.39 \leq$ OR ≤ 0.98; CIs encompassed the null value of 1.00 for all exposure categories, with 12 – 27 cases per exposure category). When the same multivariate adjusted analysis was conducted with the *low* exposure group as the referent, evidence of a moderately strong positive association with stomach cancer was observed in the highest exposure group, (OR = 2.38; 95% CI: 1.06, 5.37 with n = 27 cases) but no evidence of a significant positive association between stomach cancer and methyl bromide use was observed in the mid exposure category (OR = 1.93; 95% CI 0.85, 4.39).

Kidney Cancer

- Barry et al. (2012) evaluated the association between methyl bromide use and kidney cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.60%) reported any use of methyl bromide, and 25 were exposed kidney cancer cases. No evidence of a significant positive association was observed for kidney cancer at any exposure level for intensity-weighted lifetime days of exposure ($0.78 \leq$ RR ≤ 1.16; all CIs encompassed the null value of 1 for all exposure categories, with n = 7 – 9 cases per exposure category, with a p-trend = 0.51) and no evidence of a positive association was observed for the intensity-weighted lifetime days of exposure with 15-year lag ($0.77 \leq$ RR ≤ 0.90; all CIs encompassed the null value of 1 for all exposure categories, with n = 6 – 7 cases per exposure category, with a p-trend = 0.81).

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[16] The unconditional logistic regression controlled for age, sex, duration of union affiliation, and start date of first union affiliation.
[17] The quartiles of exposure (stratified by pounds of use) for methyl bromide included: 0lbs, 1 – 133, 134 – 4,856, and 4,857– 280,130.

Cancers of the Intestines

Several AHS studies evaluated methyl bromide exposure and cancers of the intestines colon, rectal, and colorectal cancers. These are summarized below.

Rectal Cancer

The association between methyl bromide exposure and rectal cancer was evaluated in t AHS studies (Lee et al., 2007; Barry et al., 2012) described below.

- The association between rectal cancer and specific pesticides including methyl bromide was evaluated by Lee et al. (2007). The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina, enrolled in the AHS cohort. Cases were identified using cancer registry files from Iowa and North Carolina and identified through the International Classification of Diseases for Oncology (ICD-0-2) code and controls included pesticide applicators (males only) who had not been previously diagnosed with rectal cancer. Vital status was confirmed through the state death registries and the National Death Index annually. Incident cases were determined beginning at study enrollment (1993-1997) through December 31, 2002. Exposure was assessed through an initial enrollment questionnaire and followed by a more detailed self-administered questionnaire filled out at home as part of initial enrollment. The questionnaires were used to determine pesticide usage of 50 different pesticides including methyl bromide. Exposure intensity values for individual pesticides were calculated using data collected from the questionnaire completed at enrollment as well as information obtained from previous published literature on pesticides. An unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures, and was adjusted for age, smoking status, state, and total days of pesticide application among all enrolled study participants. Of the 93 rectal cancer cases, 18 cases reported ever having exposure to methyl bromide, while 71 cases reported never having exposure to methyl bromide. The study authors reported no evidence of a significant positive association between rectal cancer and exposure to methyl bromide, based on ever-use (OR = 1.10; 95% CI: 0.60, 2.10).

- Barry et al. (2012) evaluated the association between methyl bromide use and rectal cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 28 were exposed rectal cancer cases. No evidence of a significant positive association was observed for colon cancer at any exposure level for either intensity-weighted lifetime days of exposure ($0.69 \leq RR \leq 1.38$; all CIs encompassed the null value of 1 for all exposure categories, with 5 – 10 cases per exposure category, with a p-trend = 0.48) or the intensity-weighted lifetime days of exposure with 15-year lag ($0.56 \leq RR \leq 1.43$; all CIs encompassed the null value of 1 for all exposure categories, with n = 4 – 8 cases per exposure category, with a p-trend = 0.52).

Colon Cancer

The association between methyl bromide exposure and colon cancer was evaluated in three AHS studies (Lee et al., 2007; Andreotti et al., 2010; Barry et al., 2012) described below.

- The association between colon cancer and specific pesticides including methyl bromide was evaluated by Lee et al. (2007). The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina, enrolled in the AHS cohort. Incident cases were determined through state cancer registry files from enrollment (1993-1997) through December 31, 2002 and vital status was confirmed through the state death registries and the National Death Index. Controls included pesticide applicators (males only) who had not been previously diagnosed with colon cancer. Pesticide exposure was assessed through an initial enrollment questionnaire and a more detailed self-administered questionnaire filled out at home as part of initial enrollment. The questionnaires were used to determine pesticide usage of 50 different pesticides including methyl bromide. Exposure intensity values for individual pesticides were calculated using data collected from the questionnaire completed at enrollment as well as information obtained from previous published literature on pesticides. An unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures, and was adjusted for age, smoking status, state, and total days of pesticide application among all enrolled study participants. Of the 212 colon cancer cases, 43 cases reported ever having exposure to methyl bromide, while 155 cases reported never having exposure to methyl bromide. The study authors reported no evidence of a significant positive association between colon cancer and ever exposure to methyl bromide, based on ever-use (OR = 1.30; 95% CI: 0.90, 2.10).

- Andreotti et al. (2010) investigated the interaction between body mass index (BMI) and pesticide exposure including methyl bromide, relative to the risk of colon cancer among men. Using data from the AHS, pesticide exposure was assessed through two self-administered questionnaires completed at study enrollment and at home. Incident colon cancer cases included male participants, living in Iowa or North Carolina, who had completed an initial and follow-up study questionnaire for the AHS, and self-reported diagnosis with colon cancer between study enrollment and December 31, 2005. Cancer cases were ascertained through the state cancer registries, and vital status was confirmed through the National Death Index and state death registries. Cox proportional hazard regression was used to calculate HRs and 95% CIs for colon cancer incidence and BMI and to determine whether an interaction between BMI and pesticide exposures existed. As the focus of this study was on the interaction between BMI and methyl bromide exposure relative to the risk of colon cancer, we cannot not draw any conclusions from this study.

- Barry et al. (2012) evaluated the association between methyl bromide use and colon cancer in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.60%) reported any use of methyl bromide, and 67 were exposed colon cancer cases. Evidence of a positive association was reported for colon cancer and intensity-weighted lifetime days of exposure for low use (> 0 – 310 days of use: RR = 1.57: 95% CI, 1.02, 2.41, with n = 27 cases). No evidence of a

significant positive association was observed for colon cancer at any other exposure level for intensity-weighted lifetime days of exposure ($0.68 \le RR \le 1.63$; all CIs encompassed the null value of 1 for all other exposure categories, with 7 – 15 cases per exposure category, with a p-trend = 0.77) or for colon cancer at any exposure level for the intensity-weighted lifetime days of exposure with 15-year lag ($0.76 \le RR \le 1.28$; all CIs encompassed the null value of 1 for all exposure categories, with 6 – 18 cases per exposure category, with a p-trend = 0.67).

Colorectal Cancer

- The association between colorectal cancer and specific pesticides including methyl bromide was evaluated by Lee et al. (2007) using data from the AHS. The study population (n = 56,813) consisted of male pesticide applicators and their spouses living in Iowa and North Carolina who were enrolled in the AHS cohort. Cases were identified using cancer registry files from Iowa and North Carolina state cancer registries and through the International Classification of Diseases for Oncology (ICD-0-2) code and controls included pesticide applicators (males only) who had not been previously diagnosed with colorectal cancer. Vital status was confirmed through the state death registries and the National Death Index annually. Incident cases were determined beginning at study enrollment (1993-1997) through December 31, 2002. Pesticide exposure was assessed through an initial enrollment questionnaire and followed by a more detailed self-administered questionnaire filled out at home as part of initial enrollment. Exposure intensity values for individual pesticides were calculated using data collected from the questionnaire completed at enrollment as well as information obtained from previous published literature on pesticides. An unconditional logistic regression was used to calculate ORs and 95% CIs for individual pesticide exposures, and was adjusted for age, smoking status, state, and total days of pesticide application among all enrolled study participants. Of the 305 colorectal cancer cases, 61 cases reported ever having exposure to methyl bromide, while 226 cases reported never having exposure to methyl bromide. The study authors reported no evidence of a significant positive association between colorectal cancer and exposure to methyl bromide, based on ever-use (OR = 1.30; 95% CI: 0.90, 1.80).

Lymphohematopoietic Cancers

- Barry et al. (2012) evaluated the association between methyl bromide use and lymphohematopoietic cancers (which includes non-Hodgkin lymphoma (NHL), leukemia, Hodgkin lymphoma, and multiple myeloma) in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 68 were exposed lymphohematopoietic cancer cases. Evidence of a positive association was observed for lymphatic-hematopoietic cancers at only the low use exposure level for intensity-weighted lifetime days of exposure (RR = 1.60; 95% CI:1.08, 2.37, with n =33 cases). No evidence of a positive association or a significant exposure-response trend was observed for lymphohematopoietic cancers at any other exposure level for intensity-weighted

lifetime days of exposure (0.63 ≤ RR ≤ 0.77, all CIs encompassed the null value of 1 for all other exposure categories, with n = 7 – 20 cases, p-trend = 0.17) and no evidence of a significant positive association was observed for any exposure categories in the intensity-weighted lifetime days of exposure with 15-year lag (0.63 ≤ RR ≤ 1.38, all CIs encompassed the null value of 1 for all exposure categories, with n = 6 – 24 cases, p-trend = 0.38).

Non-Hodgkin Lymphoma

The association between methyl bromide exposure and non-Hodgkin lymphoma was evaluated in two AHS studies (Barry et al., 2012; Alavanja et al., 2014) described below.

- Barry et al. (2012) evaluated the association between methyl bromide use and non-Hodgkin lymphoma (NHL) in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 35 were exposed NHL cases. Evidence of a moderately strong association was reported for NHL and intensity-weighted lifetime days of exposure for low use (RR = 2.33: 95% CI, 1.40, 3.88, with n = 21 cases); however, no evidence of a positive association or evidence of an exposure-response trend was observed for NHL at any other exposure level for intensity-weighted lifetime days of exposure (0.64 ≤ RR ≤ 0.73, all CIs encompassed the null value of 1 for all other exposure categories, with n = 6 – 8 cases, p-trend = 0.13). Neither evidence of a significant positive association for any exposure category nor evidence of an exposure-response trend was observed for intensity-weighted lifetime days of exposure with 15-year lag (0.62 ≤ RR ≤ 1.67, all CIs encompassed the null value of 1 for all other exposure categories, with n = 6 – 13 cases, p-trend = 0.74).

- Alavanja et al. (2014) investigated the association between methyl bromide and non-Hodgkin lymphoma (NHL) and various NHL-subtypes among pesticide applicators in the AHS living in Iowa and North Carolina. This analysis excluded pesticide applicators who reported a history of any cancer at time of enrollment who were missing information on potential confounders and any who did not live in the catchment area at time of registration. Cases were AHS participants with incident NHL or NHL subtypes diagnosed at enrollment (1993 – 2007) through December 2010 in North Carolina and through December 2011 in Iowa. Tumor information was obtained through cancer registry files in Iowa and North Carolina through 2010 (in North Carolina) and 2011 (in Iowa). Pesticide exposure was assessed via self-administered questionnaires during study enrollment and a second telephone questionnaire administered five years after enrollment (1999 – 2005). Investigators used questionnaire data, monitoring, and literature to estimate lifetime-days and intensity-weighted lifetime days of pesticide use. For the 37% of participants that did not complete follow-up questionnaire, authors used a data-driven multiple imputation procedure with logistic regression and stratified sampling to impute missing pesticide usage information. The responses to both questionnaires and imputed data and an intensity exposure- algorithm were used to determine cumulative exposure metrics: lifetime days of pesticide use, intensity-weighted lifetime days of use and

ever/never use data for each pesticide. For both lifetime days and intensity-weighted lifetime days analysis, the following categories were created: low ($\leq$ 8 days), medium (> 8 – 28 days), and high (> 28 – 387.50 days), and RRs and 95% CIs were reported for each category with no exposure as the referent. Poisson and polytomous models were used to calculate RRs and 95% CIs, controlling for age, race, state, and total days of herbicide use. Among the 54,306 participants, there were 523 incident NHL cases and 85 NHL cases who reported exposure to methyl bromide. For overall NHL, no evidence of a significant positive association between methyl bromide and risk of NHL (RR = 1.10; 95% CI: 0.90, 1.50) was observed, based on ever/never use of methyl bromide. For the analysis of lifetime days of use for overall NHL, evidence a moderately strong positive association was observed for the low exposure category (RR = 2.00; 95% CI: 1.40, 2.90, with 37 exposed cases) only and evidence of a positive association was observed for the low exposure category for intensity-weighted lifetime days of use (RR = 1.80; 95% CI: 1.20, 2.70, with n = 26 cases) only. No evidence of a significant positive association was observed in any other exposure category for either lifetime days of use ($0.60 \leq RR \leq$ 0.90, all CIs encompassed the null value of 1 for all exposure categories, with n = 17 – 24 cases, p-trend = 0.04) or intensity-weighted days of use of methyl bromide for overall NHL ($0.80 \leq RR \leq 1.10$, all CIs encompassed the null value of 1 for all exposure categories, with n = 25 cases for both categories, p-trend = 0.10). An unexpected inverse and significant exposure-response was observed for increasing exposure to methyl bromide for lifetime days of use (p-trend = 0.04) in which increased methyl bromide exposure lead to decreased NHL risk but was not significant for intensity-weighted lifetime days of use (p-trend = 0.10).

For analysis of ever/never use of methyl bromide and NHL subtypes, evidence of a positive association was observed for the NHL subtype: *diffuse large B-cell lymphomas* (RR = 1.90; 95% CI: 1.10, 3.30 with n = 28 exposed and 86 unexposed cases) based on ever/never methyl bromide use. No other NHL subtype demonstrated a significant positive association with methyl bromide, based on ever/never use: *other B-cell lymphomas* (RR = 2.2; 95% CI: 0.90, 5.70 with n = 8 exposed and 44 unexposed cases); *small B-cell lymphocytic lymphomas (SLL)/ chronic B-cell lymphocytic lymphomas (CLL)/ mantle-cell lymphomas (MCL)* (RR = 0.90; 95% CI: 0.5, 1.7 with n = 18 exposed and 126 unexposed cases); *follicular lymphomas* (RR = 0.60; 95% CI: 0.20, 1.40 with n = 7 exposed and 58 unexposed cases); or, *multiple myeloma* (RR = 1.00; 95% CI: 0.60, 1.80 with n = 19 exposed and 76 unexposed cases). In the additional analyses of the association between NHL subtypes and lifetime-days of use of methyl bromide, categories were created for low and high exposure levels, at the median of exposure, with the no exposure group serving as the referent. The low exposure categories for both of the NHL subtypes *diffuse large B-cell lymphoma* and *other B-cell lymphomas* displayed evidence of a strong association with lifetime-days of methyl bromide use (*diffuse large B-cell lymphoma*: RR = 4.00; 95% CI: 2.20, 7.40, with n = 15 exposed and 86 unexposed cases; *other B-cell lymphomas*: RR = 3.60; 95% CI: 1.30, 9.80, with n = 5 exposed and 44 unexposed cases), but these associations are based on few exposed cases. Other subtype-exposure categories did not exhibit a significant positive association with lifetime-days of methyl bromide use and no subtypes demonstrated evidence of an increasing risk of disease with increased use of methyl bromide (p-trend > 0.05 for all

NHL subtypes). Polytomous logit models indicated homogeneity across NHL subtypes (p = 0.59).

Leukemia

- Barry et al. (2012) evaluated the association between methyl bromide use and leukemia in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 20 were exposed leukemia cases. No evidence of a positive association was observed for leukemia at any exposure level for intensity-weighted lifetime days of exposure (0.60 ≤ RR ≤ 1.00, all CIs encompassed the null value of 1 for all exposure categories, with n = 5 – 8 cases, p-trend = 0.30) and no evidence of a significant positive association was observed for the intensity-weighted lifetime days of exposure with 15-year lag (0.63 ≤ RR ≤ 1.19, all CIs encompassed the null value of 1 for all exposure categories, with n = 5 – 7 cases, p-trend = 0.44).

Melanoma

- Barry et al. (2012) evaluated the association between methyl bromide use and melanoma in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 27 were exposed melanoma cases. No evidence of a significant positive association was observed for melanoma cancer at any exposure level for intensity-weighted lifetime days of exposure (0.36 ≤ RR ≤ 1.06; all CIs encompassed the null value of 1 for all exposure categories, with 5 – 16 cases per exposure category, with a p-trend = 0.06). For intensity-weighted lifetime days of exposure with 15-year lag no evidence of a significant positive association was reported for the mid exposure category (mid >310 – 1,519 days of use: OR = 1.20; 95% CI: 0.65, 2.22, with n = 14 cases), no evidence of a positive association was reported for the low and high exposure categories (low >0 – 310 days of use: RR = 0.53; 95% CI: 0.21, 1.33, with n = 5 cases; high >1,519 days of use: RR = 0.47; 95% CI: 0.18, 1.22, with n = 5 cases, p-trend = 0.17).

Oral Cavity Cancers

- Barry et al. (2012) evaluated the association between methyl bromide use and oral cavity cancers in addition to assessing all cancers (combined) and several individual cancers using data from the AHS. See above (All Cancers) for study details. Among the 53,588 applicators in the study population, 7,814 (14.6%) reported any use of methyl bromide, and 19 were exposed oral cavity cancer cases. No evidence of a significant positive association was observed for oral cavity cancer at any exposure level for either intensity-weighted lifetime days of exposure (1.27 ≤ RR ≤ 1.62, with n = 8 – 11 cases, all CIs encompassed the null value of 1 for all exposure categories, p-trend = 0.79) or the intensity-weighted lifetime days of exposure with 15-year lag (0.96 ≤ RR ≤ 1.33, all CIs

encompassed the null value of 1 for all exposure categories, with n = 6 – 8 cases, p-trend = 0.49).

Non-Carcinogenic Effects

Thyroid Disease

The association between methyl bromide exposure and thyroid disease was evaluated in five AHS studies (Goldner et al., 2010; Goldner et al., 2013; Lerro et al., 2018; Shrestha et al., 2018a; Shrestha et al., 2018b) described below.

- Goldner et al. (2010) evaluated the potential association between thyroid disease and methyl bromide and other pesticides in a cross-sectional analysis using data from the AHS. Pesticide exposure among <u>female spouses of male farmers</u> in the AHS was reported through two self-administered questionnaires at enrollment and prevalent thyroid disease status was ascertained through self-report during follow-up interviews (1999-2003). Prevalent thyroid disease was further classified into three subgroups: hypothyroidism, hyperthyroidism, and 'other' thyroid disease. Polytomous logistic regression analysis was used to analyze the association between ever-use of a pesticide and the occurrence of thyroid disease, and the model was adjusted for BMI at enrollment, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education using stepwise selection. Of the 2,043 total cases of thyroid disease reported, 2 (0.50%) hyperthyroid cases, 15 (1.30%) hypothyroid cases, and 6 (1.10%) 'other' thyroid cases reported ever-use of methyl bromide. No evidence of a significant positive association was observed for hypothyroid or 'other' thyroid disease relative to methyl bromide exposure (OR = 1.60; 95% CI: 0.92, 2.80 for hypothyroid; OR = 1.30; 95% CI: 0.556, 2.90 for 'other' thyroid), respectively. No OR was reported for hyperthyroid disease and methyl bromide exposure as fewer than 5 cases oh hyperthyroid disease reported exposure to methyl bromide.

- In a separate study, Goldner et al. (2013) evaluated the potential association between prevalent thyroid disease, specifically hypothyroid disease, and methyl bromide and other pesticides among <u>male pesticide applicators</u> who were enrolled in the AHS. Pesticide exposure was reported through two self-administered questionnaires at enrollment (1993 – 1997), and thyroid disease status was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003) and Phase III (2005 – 2010) of the study. Logistic regression was used to analyze the association between ever-use of methyl bromide and the occurrence of thyroid disease, adjusting for BMI, age at enrollment, and education. Of the 22,246 AHS study participants, a total of 461 hypothyroid cases were reported, and 51 (11.10%) of these cases reported ever-use of methyl bromide. Of the 21,327 pesticide applicators reporting no thyroid disease with complete data, 2,752 (12.90%) reported ever-use of methyl bromide. The study reported suggested no evidence of a positive association between hypothyroid disease and exposure to methyl bromide (OR = 0.81; 95% CI: 0.60, 1.09), based on ever/never use among male pesticide applicators.

- Lerro et al. (2018) conducted a cohort study using data from AHS participants in the subset study Biomarkers of Exposure and Effect in Agriculture (BEEA), to investigate the association between hypothyroidism among private pesticide applicators exposed to pesticides including methyl bromide. The BEEA was conducted from June 2010 to September 2013 and cases included male pesticide applicators who were part of the AHS and lived in North Carolina or Iowa and were ≥ 50 years of age at enrollment for BEEA with no previous diagnosis of cancer (besides non-melanoma skin cancer). Additionally, cases must have completed the AHS questionnaires at enrollment (1993 – 1997) and follow-up (1999 – 2003, 2005 – 2010), not have a history of clinical thyroid disease, and not taking thyroid medications. Non-fasting blood samples were collected by a trained phlebotomist and serum samples were measured to confirm subclinical hypothyroidism in each case. Subclinical hypothyroidism was defined as thyroid-stimulating hormone (TSH) levels > 4.5 mIU/L (normal thyroid function defined as having TSH levels of 0.4-4.5 mIU/L).[18] Pesticide exposure was assessed via the study questionnaires completed at enrollment and during follow-up of the AHS, and exposure data on frequency (average days/year) and duration (years) of use for select pesticides including methyl bromide was obtained. Intensity-weighted lifetime exposure days were calculated for each pesticide by multiplying lifetime exposure days by an intensity-weighted factor. Multivariable logistic regression was performed to determine ORs and 95% CIs for the association of intensity-weighted days of specific pesticides including methyl bromide with subclinical hyperthyroidism controlling for age, smoking, state, BMI, and correlated pesticides. No evidence of a significant positive association was observed at either the low or high exposure levels to methyl bromide relative to the non-exposed group for subclinical hypothyroidism (12 – 1,139 days: OR = 1.32; 95% CI: 0.44, 4.02, with 6 cases; > 1,139 – 102,000 days: OR = 0.45; 95% CI: 0.11, 1.81, with 3 cases, with a p-trend = 0.23).

- Shrestha et al. (2018a) evaluated the association between thyroid disease and exposures to pesticides including methyl bromide. The study population consisted of <u>female spouses of pesticide applicators</u> enrolled in the AHS, an ongoing, prospective cohort study. Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997), and thyroid disease, both hyperthyroid and hypothyroid disease status, was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III (2005 – 2010) and Phase IV (2013 – 2016) of the study. Validation of self-reported cases of hyperthyroid and hypothyroid disease was carried out using medical record data. The Cox proportional hazards model was used to calculate separate HRs for hypothyroid and hyperthyroid disease, controlling for smoking, education, state, and correlated pesticides. Authors used multiple imputation with fully conditional specification method to impute missing covariates for 1,273 spouses missing information on smoking status and 3,106 on education. Of the 24,092 female spouses of pesticide applicators in the study population, 1,627 had hypothyroid disease, 531 had hyperthyroid disease, and 21,934 were noncases. No evidence of a significant positive association was reported for hypothyroid disease relative to ever-use of methyl bromide in female spouses of pesticide applicators (HR = 1.02; 95% CI: 0.64, 1.62 with n = 18 exposed cases, 1,542 unexposed cases). When the data was further adjusted for correlated pesticides (correlation coefficient > 40%): Metalaxyl (0.41), no evidence of a positive association

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[18] LeFevre ML; U.S. Preventive Services Task Force. Screening for thyroid dysfunction: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015; 162:641–50.

was reported for hypothyroid disease (HR = 0.75; 95% CI: 0.44, 1.28). An additional analysis that restricted thyroid cases to those female spouses who received treatment, reported no evidence of a significant positive association for hypothyroid disease relative to ever exposure to methyl bromide (HR = 1.06; 95% CI: 0.64, 1.74 with n = 16 exposed cases, 1,380 unexposed cases). An additional analysis that only included thyroid cases which were validated according to the stricter case definition standards (ascertained via medical record data; confirmed via validation questionnaire; reported thyroid disease at least twice in follow-up surveys) similarly reported no evidence of a positive association for hypothyroid disease relative to methyl bromide exposure was observed (HR = 0.95; 95% CI: 0.47, 1.93 with n = 8 exposed cases, 812 unexposed cases). For hyperthyroid disease, authors did not report any data on the potential association of hyperthyroid disease and exposure to methyl bromide.

- In a separate study Shrestha et al. (2018b) evaluated the potential association between incident hypothyroidism and methyl bromide and other pesticide exposure in a cohort study of <u>pesticide applicators</u> who were enrolled in the AHS. Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997), and incident thyroid disease, both hyperthyroid and hypothyroid disease status, was ascertained through self-report during follow-up interviews during Phase II (1999 – 2003), Phase III (2005 – 2010) and Phase IV (2013 – 2016) of the study. Validation of self-reported cases of hyperthyroid and hypothyroid disease was carried out using medical record data. The Cox proportional hazards model was used to estimate HRs and 95% CIs for associations with pesticides, including methyl bromide and hypothyroidism, controlling for sex, education, state, and smoking. Participants in the final sample included 35,150 male and female pesticide applicators who completed the enrollment questionnaire and at least one follow-up survey; 829 of these had hypothyroid disease, 271 had hyperthyroidism, and 34,050 participants did not have thyroid disease. For the analysis of ever exposure to methyl bromide and hypothyroid disease, no evidence of a positive association was reported (HR = 0.96; 95% CI: 0.76, 1.21 with n = 113 exposed cases). When the data for ever exposure to methyl bromide were further adjusted for the correlated pesticide metalaxyl[19], similar results were reported (HR = 0.93; 95% CI: 0.72, 1.22). An additional analysis using intensity-weighted lifetime days for methyl bromide using the following tertiles of intensity-weighted days: $> 0 – \leq 320$; $>320 – \leq 1,372$; and $> 1,372$; and compared to the referent group of no exposure, no evidence of a significant positive association was observed for any exposure level ($0.88 \leq HR \leq 1.09$; all CIs encompassed the null value of 1; n = 32 – 42 cases per tertile; p-trend = 0.44). When data for intensity-weighted lifetime days for methyl bromide use and hypothyroidism were further adjusted for the correlated pesticide metalaxyl, similar results were reported ($0.87 \leq HR \leq 1.06$; all CIs encompassed the null value of 1; p-trend = 0.46). When analysis of hypothyroidism and ever use of methyl bromide was restricted to hypothyroid cases taking thyroid-related medications, no evidence of a positive association was observed for hypothyroidism relative to ever-use of methyl bromide (HR = 0.98; 95% CI: 0.76, 1.25, with n = 102 exposed cases). Similar results were observed for the analysis of ever-use of methyl bromide and hypothyroidism when female applicators were excluded

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[19] Correlated pesticide (correlation coefficient $\geq$ 0.40) included: Metalaxyl.

(HR = 0.94; 95% CI: 0.73, 1.20, with n = 106 exposed cases). Further analysis of ever-use of methyl bromide and hypothyroidism risk, when cases were restricted to those confirmed by the study standards[20] reported no evidence of a significant positive association (HR = 1.29; 95% CI: 0.89, 1.87, with n = 49 exposed cases).   Finally, when the association between ever/never use of methyl bromide and hypothyroidism among pesticide applicators was analyzed using inverse probability of censoring weights to investigate the impact of loss to follow-up, no evidence of a positive association was observed (HR = 0.99; 95% CI: 0.77, 1.26, with n = 113 exposed cases).

Parkinson's Disease

- Kamel et al. (2007) evaluated the association between exposure to pesticides including methyl bromide and Parkinson's disease (PD). Using data from the AHS, the study sample population included pesticide applicators and their spouses living in Iowa and North Carolina. Cases were defined as participants who self-reported physician-diagnosed PD at enrollment between 1993 and 1997 (prevalent cases, n = 83) or during a follow-up telephone interview conducted between 1999 and 2003 (incident cases, n = 78). Cases were compared with cohort members who did not report PD (n = 79,557 at enrollment and n = 55,931 at follow-up). Hierarchical regression models were used to calculate ORs and 95% CIs for risk of PD and individual pesticides including methyl bromide based on ever/never use and were adjusted for age, state, and type of participant (applicator or spouse). Of the 83 cases reporting prevalent PD, 6 (8%) reported exposure to methyl bromide and of the 79,557 controls, 7,891 (10%) reported exposure to methyl bromide. Of the 78 incident PD cases, 10 (13%) reported exposure to methyl bromide while 5,455 (10%) of 55,931 controls reported exposure to methyl bromide. In the pesticide specific logistic regression model there was no evidence of a positive association between ever exposure to methyl bromide and prevalent PD (OR = 0.90; 95% CI: 0.40, 2.20) and no evidence of a significant positive association between ever exposure to methyl bromide and incident PD (OR = 2.10; 95% CI: 0.90, 4.90).

Dream Enacting Behavior

- Shrestha et al. (2018c) examined the association between exposure to pesticides including methyl bromide and risk of dream enacting behavior (DEB) among male pesticide applicators in the AHS. Rapid-eye movement (REM) sleep behavior disorder (RBD), characterized by loss of muscle atonia during REM sleep and the presence of DEB is thought to be rare in the general population but very common among patients with Parkinson's disease (PD) and other neurodegenerative diseases (multiple system atrophy, dementia with Lewy bodies). RBD is believed to be a specific prodromal symptom of these conditions, with as many as 80% of RBD patients eventually developing one of these diseases and AHS farmers who reported DEB were 8 times more likely to report PD diagnosis).[21] Study participants included male pesticide applicators in the AHS living

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[20] Study standards restricted cases in this analysis who were a.) ascertained via medical record data b.) confirmed via the validation questionnaire or c.) reported hyperthyroidism or hypothyroidism at least twice in the AHS surveys.
[21] Shrestha, S., et al. (2017). "Nonmotor symptoms and Parkinson disease in United States farmers and spouses." PLoS One 12(9): e0185510.

in Iowa and North Carolina who completed a follow-up interview that screened for several PD prodromal symptoms including DEB, conducted between 2013 and 2015. Cases were compared with cohort members who also completed the follow-up interview but did not report DEB (n = 16,441). Pesticide exposure was reported through self-administered questionnaires at enrollment (1993 – 1997), and physician diagnosis of PD was ascertained through self-report during follow-up interviews and validated using medical record data. Multivariable logistic regression was used to calculate ORs and 95% CIs, adjusting for age, smoking, alcohol consumption, marital status, education, state, and head injury. Authors used inverse probability weighting to impute missing data to account for the loss of participants and loss of covariates as 23,478 (46%) of the 51,035 male farmers in AHS completed the follow-up survey (2013-2015). Of the 20,591 male farmers, 1623 (7.90%) self-reported DEB during the follow-up interview and 1,001 of these also reported experiencing DEB symptoms $\geq$ 3 times. Results showed no evidence of a positive association between methyl bromide exposure and DEB (OR = 1.00; 95% CI: 0.80, 1.20, with n = 202 cases). In a further analysis that excluded PD patients, no evidence of a positive association was observed between DEB and ever-use of methyl bromide (OR = 1.00; 95% CI: 0.80, 1.30, with n = 197 cases). And in a further analysis that defined DEB cases as reporting symptoms $\geq$ 3 times in a lifetime, no evidence of a positive association was observed between DEB and ever-use exposure to methyl bromide (OR = 0.90; 95% CI: 0.70, 1.20, with n = 109 cases).

Eye Disorders

The association between methyl bromide exposure and eye disorders was evaluated in two AHS studies (Kirrane et al., 2005; Montgomery et al., 2017) described below.

- Using data from AHS, Kirrane et al. (2005) investigated the association of pesticide exposures, including methyl bromide and retinal degeneration and other eye disorders among female spouses of pesticide applicators in the AHS in a cross-sectional study. A total of 31,173 women self-reported eye disorders and pesticide use through mailed questionnaires (1993-1997) which were completed and returned by study participants; however, telephone interviews were used for the subjects who did not return their mailed questionnaire. Logistic and hierarchical logistic regression modeling were used to obtain ORs and 95% CIs for individual pesticides including methyl bromide, controlling for age and state of residence. Of the 281 cases who reported retinal or macular degeneration among the study participants, 1.10% reported exposure to methyl bromide, and among the controls, 1.20% reported exposure to methyl bromide. Results showed no evidence of a positive association between methyl bromide exposure and retinal degeneration (OR = 0.90; 95% CI: 0.40, 2.20).

- Montgomery et al. (2017) conducted a case-control study nested within the AHS to determine if incident cases of age-related macular degeneration (AMD) were associated with previous exposure to pesticides, including methyl bromide. Using data from the AHS follow-up interviews, cases included AHS pesticide applicators (men and women) and spouses who were >50 years old and who self-reported either an incident AMD diagnosis between 1994 and September 2007 or early signs of AMD. Cases were

ascertained by physicians with supporting pathology or retinal photographs obtained from the cases. Cases were compared to a control group, consisting of AHS members who did not have AMD. Pesticide exposure was assessed at enrollment via self-report. Logistic regression analysis was used to determine ORs and 95% CIs, controlling for age, gender, and smoking. Among the 161 cases and 39,108 controls, 17 (11%) cases and 4,106 (11%) controls reported exposure to methyl bromide. In the analysis of the association between ever/never exposure to methyl bromide and incident AMD among pesticide applicators and their spouses, no evidence of a positive association was observed (OR = 0.80; 95% CI: 0.50, 1.40). For select pesticides including methyl bromide, pesticide applicators provided additional details such as frequency and duration of use during the exposure assessment. Exposure duration was categorized by cumulative days of exposure, and individual ORs and 95% CIs were calculated for each category, adjusting for smoking and age. For methyl bromide, the exposure levels were >0 – 10 and >10 cumulative days of use. In the exposure-response analysis of lifetime days of use of methyl bromide, using methyl bromide specific exposure levels, no evidence of a significant positive association relative to AMD at either exposure level was observed (>0 – 10 days: OR = 1.20; 95% CI: 0.50, 2.90, with 6 cases, 923 controls; >10 days: OR = 0.80; 95% CI: 0.40, 1.50, with 11 cases, 2,728 controls, with a p-trend = 0.582).

Suicide

- Beard et al. (2011) evaluated the potential association between suicide and pesticide exposure, including methyl bromide using data from the AHS. Pesticide exposure was assessed via a self-administered questionnaire at enrollment. Cases (suicides after enrollment) were identified by linking the AHS cohort to state mortality files and the National Death Index through May 31, 2009. The Cox proportional hazards model was used to analyze the association between pesticide exposure and suicide risk and to calculate hazard ratios (HR) and 95% CIs, adjusting for age at enrollment, sex, number of children, frequency of alcohol consumption within the past year, and smoking. Among the study population (n = 81,998), 8,095 reported methyl bromide exposure. There were 15 suicides (cases with exposure to methyl bromide) occurring between enrollment in the AHS (from 1993 to 1997) and May 2009. The study results suggest no evidence of a positive association between suicide and ever use of methyl bromide exposure among applicators and spouses (HR = 0.80; 95% CI: 0.46, 1.41). A further analysis considered cumulative lifetime days of use for specific pesticides including methyl bromide and the risk of suicide among pesticide applicators only. No evidence of a positive association was found for methyl bromide exposure at any exposure level (≤ 26 cumulative lifetime days of use HR = 0.98, 95% CI: 0.49, 1.98 with n = 9 cases; > 26 cumulative lifetime days of use HR = 0.62, 95% CI: 0.25, 1.53 with n = 5 cases; p-trend = 0.30).

Depression

The association between methyl bromide exposure and depression was evaluated in two AHS studies (Beard et al., 2013; Beard et al., 2014) described below.

- Beard et al. (2013) investigated the potential association between depression with methyl bromide and other pesticides among farmers' wives enrolled in the AHS. The study population consisted of <u>female spouses of pesticide applicators</u> (n = 16,893) in the AHS living in Iowa and North Carolina who did not report physician-diagnosed depression at enrollment and who completed a follow-up telephone interview (2005-2010). Cases included farmers' wives who self-reported incident physician-diagnosed depression between the time of study enrollment (1993-1997) and study follow-up (2005-2010) and were ascertained through responses to questions during the telephone follow-up interview. The controls included study participants who did not report incident depression. A log-binomial regression model was used to estimate RRs and 95% CIs to determine if an association between ever-use of a pesticide and depression existed. Inverse probability weights were applied to adjust for education level, age at enrollment, ever diagnosed with diabetes, state of residence, and drop out, as well as to account for the substantial number of study subjects (n = 10,639) who did not complete the follow up interview (1,342 due to death). Of the 1,054 cases reporting physician-diagnosed depression at follow-up, 16 (2%) reported exposure to methyl bromide. The study reported no evidence of a significant positive association between methyl bromide exposure and incident depression among farmer's wives based on ever/never use (RR = 1.13; 95% CI: 0.68, 1.87). A further analysis considered husbands' use of specific pesticides based on ever/never use and the risk of depression among their wives who had reported never using pesticides. For this analysis, no evidence of a significant positive association was found for methyl bromide exposure and depression (RR = 1.04; 95% CI: 0.61, 1.77 with n = 70 cases).

- Depression among AHS participants was reviewed by Beard et al. (2014) to investigate its potential association with methyl bromide and other pesticides. The study population consisted of <u>male pesticide applicators</u>. Participants self-reported physician diagnoses of depression prior to enrollment only (defined as 'PRE-E' in the study), at both enrollment and follow-up (defined as 'PRE-B' in the study), or at follow-up only (defined as 'POST' in the study). Pesticide exposure was assessed via two self-administered questionnaires at study enrollment. Polytomous logistic regression was used to calculate ORs and 95% CIs. Inverse probability weighting adjusted for confounders including age, diabetes diagnosis, education level, and state of residence and accounted for subjects missing covariate data and study drop-outs. Among the study population (n = 21,208), 1,702 (8%) reported receiving a physician's diagnosis of depression (cases). Of the 1,702 cases, 474 reported receiving a depression diagnosis at enrollment but not follow-up, and 75 (16%) of those cases reported exposure to methyl bromide. Of the 1,702 cases, 540 participants reported depression diagnosis at both enrollment and follow-up, and 90 (17%) cases reported exposure to methyl bromide. Of the 1,702 cases, 688 participants reported depression diagnosis at follow-up only, and 109 (16%) of those cases reported exposure to methyl bromide. There were 19,506 study participants who reported no physician diagnosis of depression (noncases), and 2,853 (15%) of those noncases reported exposure to methyl bromide. The study reported no evidence of a significant positive association between ever use of methyl bromide exposure and reported depression diagnosis at enrollment only (OR = 1.20; 95% CI: 0.70, 1.90), at both enrollment and follow-up (OR = 1.60; 95% CI: 1.00, 2.40), or at follow-up only among the study participants (OR = 1.20; 95% CI: 0.80, 1.80). A Wald chi-square test found no significant difference in ORs

between these groups for methyl bromide exposure (p = 0.57). In an additional analysis of cumulative lifetime days of exposure to methyl bromide, exposures were divided into the following tertiles: low exposure tertile (1-12 days), mid exposure tertile (13-54 days), and high exposure tertile (>54 days) and ORs were determined for the three case groups (diagnosis at enrollment only, diagnosis at both enrollment and follow-up, and diagnosis at follow-up only). Evidence of a positive association was observed for the highest tertile in the patient population reporting diagnosis of depression at follow-up only (high exposure tertile (>54 days): OR = 1.60; 95% CI: 1.10, 2.40, with n = 27 cases) only. No evidence of a significant positive association was observed in any other tertile for any case group (diagnosis of depression reported at enrollment only, at both enrollment and follow-up, or at follow-up only) (0.80 ≤ OR ≤ 1.60; all CIs encompassed the null value of 1; n = 18 – 43 cases per tertile; p-difference = 0.59).

Amyotrophic Lateral Sclerosis

- Kamel et al. (2012) explored the association of amyotrophic lateral sclerosis (ALS) with exposure to specific pesticides including methyl bromide through the AHS, an ongoing prospective cohort study of private pesticide applicators and their spouses. Exposure to methyl bromide and other pesticides, defined as ever use, was ascertained by self-reported questionnaires at study enrollment in the AHS (1993 – 1997). Cases of ALS were identified by state mortality files and the National Death Index and were defined as ALS listed as an underlying or contributing cause of death. Of the n = 84,739 AHS private pesticide applicators and spouses, 41 cases of ALS were identified by death certificate from enrollment through February 7, 2010, and 5 (13%) of these cases were identified as having been exposed to methyl bromide, and of the 84,698 noncases, 8,648 (11%) reported exposure to methyl bromide. Unconditional logistic regression models were used to calculate ORs and 95% CIs and were adjusted for age and gender because ALS incidence is greater in men and risk of ALS increases with increased age. The study reported no evidence of a significant positive association between ever use of methyl bromide and ALS (OR = 1.20; 95% CI: 0.50, 3.20).

Rheumatoid Arthritis

- Meyer et al. (2017) investigated the potential association between exposure to pesticides including methyl bromide and rheumatoid arthritis (RA) in male pesticide applicators in a prospective cohort study. Using data from the AHS, the study sample included male pesticide applicators enrolled in the AHS between 1993 – 1997, and who completed at least one follow-up questionnaire at any of the following time points: 1999 – 2003, 2005 – 2010, 2013 – 2015. Incident RA cases were identified and ascertained either through self-reported use of antirheumatic drugs or by physicians. Noncases included applicators who did not report RA. Exposure was assessed at enrollment and follow-up via self-report, and a logistic regression was performed to determine ORs and 95% CIs for individual pesticides including methyl bromide, controlling for age, pack-years smoking, education, and state of enrollment. Among the total incident RA cases (n = 220) and noncases (n = 26,134), 53 (24%) cases and 3,825 (15%) noncases reported exposure to methyl bromide, based on ever/never use. No evidence of a significant positive

association was observed between methyl bromide exposure and incident RA cases among male pesticide applicators (OR = 1.42; 95% CI: 0.97, 2.08). For intensity-weighted lifetime days of use, the following tertiles were used for methyl bromide (<12.25, ≥ 12.25 - <54.24, and ≥54.25) to analyze exposure-response relationships relative to RA. No evidence of a significant positive association was observed at any exposure tertile for intensity-weighted lifetime days of use and RA, with never exposure as the referent group (1.18 ≤ OR ≤ 1.74; all CIs encompassed the null value of 1; n = 16 – 19 cases/tertile; p-trend = 0.11). In an additional analysis in which the ever-use was further stratified by non-smokers vs. smokers, no evidence of a significant positive association was observed for either non-smokers or smokers (non-smokers: OR = 1.45; 95% CI: 0.83, 2.51, with 1,642 noncases and 15 cases; smokers: OR = 1.57; 95% CI: 0.98, 2.53, with 2,183 noncases, 38 cases). Similarly, no evidence of a significant positive association was observed when the data were stratified by age (age < 50 years vs. age ≥ 50 years) based on ever-use (age < 50 years: OR = 1.21; 95% CI: 0.70, 2.09, with 2,166 noncases, 26 cases; age ≥ 50 years: OR = 1.61; 95% CI: 0.94, 2.75, with 1,659 noncases and 27 cases). For incident RA cases, when possible cases (n = 160) were combined with the original number of cases reported in this study (n = 220; reported as 'probable cases') compared to the noncases, no evidence of significant positive association was observed for methyl bromide exposure based on ever/never use (OR = 1.19; 95% CI: 0.89, 1.59 with 3,825 noncases, 85 cases). No evidence of a significant positive association was observed at any exposure level and no dose-response tend was noted when incident RA (including probable and possible incident RA cases) among male licensed pesticide applicators was further stratified into tertiles of lifetime days of methyl bromide use (0.91 ≤ OR ≤ 1.49; all CIs encompassed the null value of 1 for all exposure categories; n = 20 – 35 cases per tertile; p-trend = 0.12).

Myocardial Infarction

The association between methyl bromide exposure and myocardial infarction was evaluated in two AHS studies (Mills et al., 2009; Dayton et al., 2010) described below.

- The association between myocardial infarction (MI) and pesticide usage including methyl bromide was evaluated by Mills et al. (2009) using data from the AHS, an ongoing prospective cohort study. The study population consisted of AHS male pesticide applicators living in Iowa and North Carolina, and pesticide exposure was assessed through two self-reported questionnaires completed at study enrollment. MI included both fatal and non-fatal myocardial incidents which were analyzed separately due to different follow-up times. The study population for MI mortalities (n = 54,609) was more inclusive relative to the non-fatal MI group (n = 32,024) as the non-fatal MI group only included those who completed the 5-year follow-up questionnaire (1999 – 2003). For MI mortalities, cases included pesticide applicators involved in the AHS who died from a fatal MI between the time of study enrollment to follow-up (1993-2004), and these were ascertained using state and national death databases. Non-fatal MI incident cases were identified during follow-up (1999-2003) and included AHS participants who self-reported the occurrence of MI. The Cox proportional hazard regression model was used to calculate HRs and 95% CIs for fatal and non-fatal MI risk for lifetime use of individual pesticides, adjusted for age, smoking, and state for the fatal MI analysis, and

state, age, smoking, and BMI for the non-fatal MI analysis. Among the 476 fatal MI cases, 19% reported exposure to methyl bromide, and of the 839 non-fatal MI cases, 22% reported methyl bromide exposure. No evidence of a positive association was reported for either fatal or non-fatal MI and methyl bromide exposure (fatal MI: HR= 0.83; 95% CI: 0.64, 1.08; non-fatal MI: HR = 0.97; 95% CI: 0.80, 1.17).

- Dayton et al. (2010) investigated the association of methyl bromide and other pesticide exposures and incident, non-fatal MI among female participants in the AHS. A total of 22,425 women (pesticide applicators and spouses of pesticide applicators) who completed both the enrollment questionnaire and follow-up phone interview, self-reported physician-diagnosed MI and pesticide use including methyl bromide. Logistic regression was used to calculate ORs and 95% CIs, controlling for age, BMI, smoking status, and state of residence. Of the 168 incident MI cases, 5 (3%) reported exposure to methyl bromide; of the 22,257 controls, 347 (2%) reported exposure. No evidence of a significant positive association was reported between methyl bromide exposure and MI (OR = 1.70; 95% CI: 0.70, 4.30).

Renal Disease

The association between methyl bromide exposure and renal disease was evaluated in two AHS studies (Lebov et al., 2015; Lebov et al., 2016) described below.

- Lebov et al. (2015) evaluated the association of end-stage renal disease (ESRD) and pesticides including methyl bromide. The study population consisted of <u>female spouses of pesticide applicators</u> enrolled in the AHS, an ongoing, prospective cohort study, with ESRD cases ascertained through linkage with the U.S. Renal Data System (USRDS). Of the 31,142 study participants, 98 ESRD cases were identified. Pesticide exposure was assessed by information obtained via self-administered questionnaires completed at enrollment and at home, with this information used to assess both direct exposure (wives' personal use of pesticides) and indirect exposure (husbands' ever use and cumulative use of pesticides). The Cox proportional hazards model was used to calculate HRs for ESRD, controlling for age. Exposure-response analysis of husband's cumulative use of specific chemicals accounted for the estimated amount of time that wives lived with their husbands prior to enrollment. For participants missing this information, authors imputed values based on the age-specific mean number of years that wives reported living with their husbands before enrollment. For direct exposure, 34 ESRD cases of renal disease were reported among the study participants, however there was not sufficient data to evaluate ESRD and direct exposure to certain chemicals, including methyl bromide. For the indirect exposure analysis (husbands' use of pesticides among wives' who reported no personal use of pesticides), 64 confirmed cases of renal disease were identified among study participants, and 12 (19%) of those cases reported husbands' ever use of methyl bromide. Among the 13,653 noncases, 2,105 (15.9%) controls reported husbands' ever use of methyl bromide. The study reported no evidence of a significant positive association between indirect methyl bromide exposure (husbands' use) and ESRD (HR = 1.13; 95% CI: 0.60, 2.11), based on ever/never use. For husband's cumulative lifetime days of use and ESRD among their wives, no analysis was reported for methyl bromide

because there were not sufficient numbers for evaluation (< 3 cases per exposure stratum).

- Lebov et al. (2016) evaluated the association of ESRD and pesticides including methyl bromide among <u>male pesticide applicators</u> (as opposed to the wives, above) enrolled in the AHS. ESRD cases were identified through linkage of the AHS cohort data with the US Renal Data System (USRDS). Pesticide exposure was assessed via self-administered questionnaires, and this information was used to calculate lifetime pesticide usage for 39 pesticides. Exposure values were further modified by an intensity factor to account for the variation in pesticide application practices to produce an estimate of intensity-weighted lifetime days of exposure. The Cox proportional hazards model was used to calculate HRs for ESRD, controlling for age and state of study enrollment. Of the 24,429 study participants, 320 confirmed cases of renal disease were identified. For intensity-weighted lifetime-days of exposure, tertiles of 19 exposed cases each were constructed and the following HRs were reported for each category, using the non-exposed as the referent group: low exposure tertile (< 558 days): HR = 0.65; 95% CI: 0.40, 1.06; mid exposure tertile (≥ 558 to < 1,898.75 days): HR = 0.89; 95% CI: 0.55, 1.45; high exposure tertile (≥ 1,898.75 days): HR = 0.94; 95% CI: 0.58, 1.52. No evidence of a positive association was observed between ESRD among male pesticide applicators and methyl bromide exposure in any exposure tertile and no exposure-response trend was observed (p-trend = 0.94).

Diabetes

The association between methyl bromide exposure and diabetes was evaluated in two AHS studies (Montgomery et al., 2008; Starling et al., 2014) described below.

- Montgomery et al. (2008) investigated the association between diabetes and methyl bromide exposure among <u>pesticide applicators</u>. The study population consisted of pesticide applicators in the AHS who completed both questionnaires at enrollment and follow-up (n = 33,457), and diabetes was identified via self-report on the enrollment or take-home questionnaires and during a follow-up interview completed five years after enrollment in the AHS (1999 – 2003). Questionnaire responses detailing pesticide exposure including methyl bromide were used to determine lifetime cumulative days of exposure. Multiple logistic regression was used to determine ORs and 95% CIs for the association between diabetes and methyl bromide exposure. Among the 1,176 diabetic cases, 268 (24%) reported ever use of methyl bromide and 4,621 (15%) of 30,611 non-diabetics with complete data reported ever use of methyl bromide. Evidence of a positive association was observed between ever use of methyl bromide and diabetes (OR = 1.60; 95% CI: 1.39, 1.84) when adjusted for age. However, when adjusted for age, state, and BMI, no evidence of a positive association was observed for ever-use of methyl bromide and diabetes among pesticide applicators (OR = 0.99; 95% CI: 0.84, 1.16).

- In another study, diabetes incidence among <u>female spouses of pesticide applicators</u> was reviewed by Starling et al. (2014) in a cohort study to investigate its potential association with methyl bromide and other pesticides. Using data from the AHS, the study population included female spouses (n = 13,637) of farmers who reported personally ever

mixing or applying pesticides at enrollment, with no previous diagnosis of diabetes at enrollment and completed at least one follow-up interview. Incident cases included farmers' wives who self-reported a physician-diagnosis of diabetes between study enrollment (1993 – 1997) and follow-up interviews. Pesticide exposure was assessed via self-report during study enrollment for 50 individual pesticides including methyl bromide based on ever-use. Two follow-up interviews conducted approximately every five years collected health information including incident diabetes, also via self-report. Cox proportional hazard regression models were used to estimate HRs and 95% CIs to analyze the association between ever-use of a pesticide and incident diabetes in women, with age in days as the time scale, allowing for left-truncation at age at enrolment and, adjusting for BMI and state. Of the total 688 cases, 19 (3%) reported exposure to methyl bromide, and of the total 12,949 noncases, 250 (2%) reported methyl bromide exposure. No evidence of a significant positive association was observed between methyl bromide use and incident diabetes in female spouses based on ever-use (HR = 1.21; 95% CI: 0.76, 1.94).

Fatal Injury

- Using data from the prospective cohort AHS, Waggoner et al. (2013) investigated the association between specific pesticides including methyl bromide and fatal injury among farmers. The study population consisted of AHS male farmers (n= 51,035) in Iowa and North Carolina through 2008, and individual pesticide exposure for 49 specific pesticides was assessed through the enrollment and follow-up questionnaires. Fatalities among the participants were ascertained through state death registries and the National Death Index, and cases were defined as any mortality that occurred in an occupational setting, including motor vehicle accidents, from enrollment until the end of follow-up (1993-December 31, 2008). The control group included farmers who did not suffer from a deadly injury during the study, regardless of vital status. A Cox proportional hazards model was used to calculate HRs and 95% CIs for fatal injuries and individual pesticides based on ever/never exposure, adjusted for age and state. Of the total study population (n = 51,035), 8,048 (16%) farmers reported ever exposure to methyl bromide. Among the total fatal injuries reported (n = 338), 54 (17%) reported exposure to methyl bromide. The study reported no evidence of a positive association between risk of fatal injury and methyl bromide exposure among male farmers in the AHS, based on ever/never use (HR = 0.92; 95% CI: 0.68, 1.25).

Stroke

- The risk of stroke mortality among study participants enrolled in the AHS was reviewed by Rinsky et al. (2013) to investigate its potential association with methyl bromide and other pesticides. The study population consisted of <u>male pesticide applicators</u> enrolled in the in the AHS living in Iowa and North Carolina. Pesticide exposure was assessed for 50 different pesticides including methyl bromide using self-administered questionnaires at study enrollment. Cases (n = 308) included AHS study participants who died from a stroke between study enrollment and December 31, 2008, and vital status of each case and stroke mortality, defined by underlying or contributing cause of death (ICD-9, ICD-

10) was confirmed using state death certificates. Noncases were those male participants who did not experience a stroke-related death during study follow-up. Cox proportional hazard models, with age as the time scale, were used to estimate HRs and 95% CIs adjusted for state, smoking status, and alcohol intake. Of the 308 stroke-related deaths among male pesticide applicators reported between enrollment and the end of 2008, 87 (29%) of the 308 cases and 7,488 (15%) of the 51,295 noncases reported ever use of methyl bromide. The study reported no evidence of a significant positive association between the risk of stroke mortality and methyl bromide exposure (HR = 1.21; 95% CI: 0.92, 1.60) based on ever use of methyl bromide and with the no exposure group as the referent.

Respiratory Effects

Multiple AHS studies investigated the association between methyl bromide exposure and the respiratory effects asthma, wheeze, chronic bronchitis, and rhinitis. These are summarized below.

Asthma

The association between methyl bromide exposure and asthma was evaluated in three AHS studies (Hoppin et al., 2008; Hoppin et al., 2009; Henneberger et al., 2014) described below.

- The association between adult-onset asthma among farm women and pesticide exposure including methyl bromide was investigated by Hoppin et al. (2008) in a cross-sectional analysis. The study population consisted of female participants in the AHS (n = 25,814) who completed a self-reported questionnaire or telephone interview at study enrollment (1993 – 1997), detailing pesticide usage and whether they had received a physician's diagnosis of asthma. This information was used to assess pesticide exposure to determine lifetime total years of pesticide use and to assess frequency of application. Cases were identified via self-reported physician diagnosed asthma (at age > 19 years old), with asthma cases then subdivided into atopic or non-atopic asthma based on self-reported physician-diagnosed eczema and/or hay fever. A polytomous logistic regression model was used to calculate ORs and 95% CIs for individual pesticides including methyl bromide, controlling for age, state, smoking status, BMI, and whether the subject had grown up on a farm. A total of 702 adult-onset asthma cases were identified. Among the 282 atopic asthma cases in females, 3 (1%) reported ever use of methyl bromide. Among the 420 non-atopic asthma cases, 6 (1%) reported ever use of methyl bromide; of the 25,112 subjects without asthma, 301 (1%) reported ever use of methyl bromide. For atopic asthma, an OR was not reported by the study authors due to the small number of observed cases (n < 5 cases). For non-atopic asthma, no evidence of a significant positive association for methyl bromide exposure was observed (OR = 1.21; 95% CI: 0.53, 2.77), based on ever/never use.

- Hoppin et al. (2009) investigated the association between adult-onset asthma among farmers and exposure to pesticides including methyl bromide in a cross-sectional analysis. Cases included male AHS farmers, aged ≥ 20 years old, who self-reported physician-diagnosed asthma and who completed the self-administered questionnaires

used to assess individual pesticide exposure. Investigators used this questionnaire data to estimate intensity-adjusted lifetime days of use of methyl bromide and other pesticides, and a polytomous logistic regression was used to calculate ORs and 95% CIs adjusting for age, state, smoking, BMI, and high pesticide exposure events (pesticide poisoning). Of the 19,704 private pesticide applicators who participated in this study, 127 reported atopic asthma and 314 reported non-atopic asthma. Of the 127 cases of atopic asthma, 16 (13%) cases indicated exposure to methyl bromide. Among the 314 cases of non-atopic asthma, 41(13%) cases reported methyl bromide exposure. In those who reported no asthma (n = 19,263), 2,838 (15%) reported exposure to methyl bromide. No evidence of a positive association was observed for atopic asthma or non-atopic asthma based on ever/never use (atopic asthma: OR = 0.86; 95% CI: 0.46, 1.60; non-atopic asthma: OR = 0.98; 95% CI: 0.66, 1.45). Exposure-response models were also evaluated for select pesticides including methyl bromide using intensity-adjusted lifetime days of use exposures (0, $\leq$ median, > median), and no evidence of a significant positive association was reported for either atopic and non-atopic asthma relative to methyl bromide exposure at any exposure level and no exposure-response trend (p-trend = 0.63 and p-trend = 0.62, respectively) was reported. Two additional analyses were conducted for asthma by temporarily excluding certain study participants within the study models to determine if a change in coefficients was observed. The first analysis excluded allergic AHS study participants to see if the difference in the observed results for atopic and non-atopic asthma was due to atopy alone. For methyl bromide, no evidence of a significant positive association was observed for atopy (alone) (OR = 1.06; 95% CI: 0.92, 1.23 with 359 cases), and no evidence of a positive association for either atopic or non-atopic asthma was observed (OR = 0.87; 95% CI: 0.46, 1.61, with 16 cases; OR = 0.98; 95% CI: 0.66, 1.46, with 41 cases). The second analysis temporarily removed AHS participants who reported chronic bronchitis or farmers' lung to determine if the observed results were due to asthma or another co-morbid respiratory disease. For methyl bromide, no evidence of a positive association for atopic asthma was observed (OR = 0.96; 95% CI: 0.45, 2.06 with 11 cases) and no evidence of significant positive association for non-atopic asthma was observed (OR = 1.16; 95% CI: 0.72, 1.87 with 30 cases).

- Henneberger et al. (2014) investigated asthmatic farmers enrolled in the AHS to determine if specific pesticide usage including methyl bromide contributed to exacerbating their asthma symptoms. The study population consisted of pesticide applicators living in Iowa and North Carolina who self-reported a physician diagnosis of asthma and completed both the enrollment and take-home questionnaires. Cases were a small subset of this study population (n = 926) who indicated exacerbation of asthma (self-reported visit to a hospital emergency room or doctor for an episode of wheezing or whistling during the past 12 months). Pesticide exposure was assessed via self-administered questionnaires for 36 specific pesticides including methyl bromide. A separate logistic regression model was used to calculate ORs and 95% CIs for each individual pesticide, adjusting for age (years), ever smoked, allergic status, state, and adult onset of asthma, in addition to separate indicator variables for current and past exposure. Pesticide use in this study was defined as pesticide applicators who currently use a specific pesticide, as well as non-current users who have reported past usage of a specific pesticide. Among the 926 pesticide applicators with active asthma, 202 (22%) reported asthma exacerbation in the past 12 months and 724 did not report exacerbated

asthma following pesticide exposure. Of the 202 cases, 170 (3%) cases indicated current exposure to methyl bromide. Of the 724 noncases, 638 reported exposure to methyl bromide. No evidence of a positive association between exacerbated asthma and methyl bromide exposure was observed (OR = 0.60; 95% CI: 0.20, 1.90).

Wheeze

The association between methyl bromide exposure and wheeze was evaluated in two AHS studies (Hoppin et al., 2002; Hoppin et al., 2006) described below.

- AHS investigators (Hoppin et al., 2002) explored the association between exposure to methyl bromide and other pesticides in the last year and the prevalence of wheeze among farmers. Exposure and health outcomes were ascertained through participant self-administered questionnaires. Logistic regression models were adjusted for age, state, past smoking, current smoking, and asthma/atopy. Of the 20,468 participants in the study, 3,838 reported wheeze and 16,630 participants did not report wheeze. Of the 3,838 cases, 5.70% reported exposure to methyl bromide. For the 16,630 participants who did not report wheeze, 4.2% reported exposure to methyl bromide. No evidence of a significant positive association between wheeze in the past year and methyl bromide exposure was reported (OR = 1.11; 95% CI: 0.00, 1.35).

- Hoppin et al. (2006) investigated potential associations between the use of methyl bromide and other pesticides and the prevalence of wheeze in cross-sectional analysis. Study participants were farmers (n = 17,920) and commercial pesticide applicators (n = 2,255) enrolled in the AHS between 1993 and 1997. Exposure and health outcomes were ascertained through two self-administered questionnaires at enrollment. Cases were defined as participants who reported episodes of wheezing or whistling in the chest in the year before study enrollment. Exposure was defined as pesticide use in the 12 months before enrollment ("current use"). Investigators explored the association between methyl bromide and wheeze via base logistic regression models controlling for age, BMI, smoking, asthma/atopy and previous use of pesticide (use but not in the past year). State was also included as a potential confounder in the analyses for farmers; commercial applicator participants resided only in one state (Iowa). All models for commercial applicators control for use of the chemical chlorimuron-ethyl which had a confounding effect on all other pesticides in the commercial applicator study population. Among the total farmers and commercial applicators, the study authors reported 19% of farmers and 22% of commercial applicators reported wheeze in the past year. The authors noted that 4% of farmers and 1% of commercial applicators reported current use (defined as use within the past year) of methyl bromide, 11% of farmers and 2% of commercial applicators reported former use, and 85% of farmers and 96% of commercial applicators reported never using methyl bromide. No evidence of a significant positive association was observed for wheeze among farmers relative to methyl bromide exposure (OR = 1.14; 95% CI: 0.92, 1.41). Authors did not report an OR for wheeze relative to methyl bromide exposure for commercial applicators due to the small number of observed cases (n < 5 cases).

Chronic Bronchitis

The association between methyl bromide exposure and chronic bronchitis was evaluated in two AHS studies (Hoppin et al., 2007; Valcin et al., 2007) described below.

- Hoppin et al. (2007) evaluated the potential association between chronic bronchitis and exposure to pesticides including methyl bromide in a cross-sectional study for the pesticide applicators in the AHS. The study population (n = 20,908) included applicators who lived in Iowa or North Carolina and participated in the AHS. Cases included private pesticide applicators (males only) who self-reported physician diagnosis of chronic bronchitis after age 19 and had completed both initial and follow-up study questionnaires. A logistic base model was used to calculate ORs and 95% CIs for chronic bronchitis and individual pesticides based on ever/never exposure, controlling for state, age, gender, and pack years of smoking. Among the total 654 cases and 20,254 controls, 17% of cases and 15% of noncases reported exposure to methyl bromide. The study reported no evidence of a positive association between methyl bromide exposure and chronic bronchitis among male pesticide applicators (OR = 0.91; 95% CI: 0.72, 1.17).

- In another study, Valcin et al. (2007) investigated occupational risk factors for chronic bronchitis among women in the AHS using a cross-sectional analysis of participant enrollment data. The 21,541 study participants were non-smoking female spouses of pesticide applicators. Participant-administered questionnaires determined the exposure (methyl bromide), health outcome (self-report of physician-diagnosed chronic bronchitis), and potential confounders. A logistic regression was used to calculate individual ORs and 95% CIs for specific pesticides including methyl bromide, controlling for age and state, and for other correlated pesticides in an additional model. Of the 583 cases of prevalent chronic bronchitis, 2% reported ever exposure to methyl bromide and of the 20,958 controls, 1% reported ever exposure to methyl bromide. Results showed evidence of a positive association between prevalent chronic bronchitis and lifetime methyl bromide exposure among female spouses of pesticide applicators (OR = 1.82; 95% CI: 1.02, 3.24) when adjusted by age and state.

Rhinitis

- Slager et al. (2009) investigated the association of methyl bromide and other pesticides among commercial pesticide applicators with current rhinitis through a cross-sectional analysis of the AHS cohort. The 2,245 commercial applicators from Iowa completed two self-administered questionnaires at and shortly after enrollment that assessed exposure to pesticides in the past 12 months and the outcome of current rhinitis (report of stuffy, itchy, or runny nose in the past 12 months). Logistic regression models were used to calculate ORs and 95% CIs to analyze the association between ever-use of a pesticide in the past year and current rhinitis. Models were adjusted for age, education, and growing up on a farm. A total of 1,664 individuals self-reported current rhinitis and of these, 20 (1%) reported exposure to methyl bromide. Of the 581 respondents who reported no current rhinitis, 6 (1%) reported exposure to methyl bromide. Results showed no evidence of a significant positive association between exposure to methyl bromide and rhinitis based on current use (OR = 1.04; 95% CI: 0.40, 2.66). Exposure response was not assessed for methyl bromide due to small numbers of exposed individuals.

Epidemiology Conclusion

A total of 44 published epidemiologic studies on the association between methyl bromide exposure and adverse health outcomes were reviewed for this updated Tier I Review. This includes 41 studies from the AHS and three additional studies that were identified for EPA's previous 2013 scoping assessment. Based on review of these studies, there is insufficient evidence to suggest a clear associative or causal relationship between exposure to methyl bromide and carcinogenic and non-carcinogenic health outcomes evaluated in the AHS and other study populations identified.[22] A discussion of findings on carcinogenic and non-carcinogenic effects is provided below.

Carcinogenic Effects

- AHS studies reported no evidence of a significant positive association between methyl bromide exposure and all cancers, bladder cancer, lung cancer, breast cancer, kidney cancer, rectal cancer, colorectal cancer, leukemia, melanoma, and oral cavity cancer.

- Studies on prostate cancer, stomach cancer, colon cancer, lymphohematopoietic cancers, and NHL reported evidence of a at least one positive association with methyl bromide. These findings are further characterized below:

  - For prostate cancer, five studies investigated the association between methyl bromide exposure and prostate cancer among the AHS study cohort. Alavanja et al. (2003) initially reported a link between methyl bromide and prostate cancer (Alavanja et al. 2003); however, these findings were not replicated in more recent follow-up investigators of the AHS cohort (Barry et al. 2012, Barry et al. 2011, Koutros et al. 2011, Koutros et al. 2013). EPA's 2013 scoping assessment identified two additional studies that examined California agricultural workers (Mills and Yang, 2003) and residents (Cockburn et al., 2011).[11] Mills and Yang (2003) was based on a cohort of farm workers who were part of the United Farm Workers of America and reported no evidence of a significant positive association between prostate cancer and methyl bromide among farm workers in California. Cockburn et al. (2011) conducted a population-based case control study and reported evidence of a positive association between residential proximity to agricultural fields treated with methyl bromide and prostate cancer (OR = 1.62, 95% CI: 1.02, 2.56) based on ever/never exposure. However, when exposure was stratified between high and low exposure, evidence of a positive association was reported for only the low level of exposure (OR = 1.81, 95% CI: 1.03, 3.18) and no evidence of a significant positive association was observed at the high level (OR = 1.45, 95% CI: 0.82, 2.57), nor was there evidence of a dose-response relationship (p-trend = 0.10).

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[22] Causality as defined by the Bradford Hill considerations: strength of association, consistency of evidence, specificity of the association, temporality, dose-response, biological plausibility, and coherence with established knowledge. Via Hill, Austin Bradford. "The environment and disease: association or causation?" Proceedings of the Royal society of Medicine 58.5 (1965): 295.

Overall, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and prostate cancer. AHS reported an association in an early study by Alavanja et al. (2003), but this association was not observed after more extensive follow-up of the AHS cohort. Results from other studies are mixed and relied on more limited methods to assess indirect exposure using California pesticide use record information.

o For stomach cancer, two studies reported evidence of an association between methyl bromide and gastric cancer (Barry et al., 2012; Mills and Yang, 2007). Barry et al. (2012) assessed intensity-weighted methyl bromide exposure in AHS and reported a three-fold increased risk of stomach cancer comparing the high methyl bromide exposure group to the non-exposed group (OR 3.13, 95% CI 1.25, 7.80). They further examined the potential dose response relationship and reported a significant monotonic increase in risk by increasing exposure (p-trend = 0.02). Earlier, Mills and Yang (2007) reported evidence of an association between methyl bromide exposure and stomach cancer (4th quartile versus lowest methyl bromide exposure category – OR = 2.38, 95% CI 1.06, 5.37) in a semi-ecological, nested case-control study of California farm workers. However, an attenuated magnitude was observed when comparing the upper methyl bromide group to the non-exposed group (4th quartile versus non-exposed OR = 1.33, 95% CI: 0.67, 2.67). This is an unexpected finding because typically when comparing an association with the low exposure group as the referent, the risk estimate decreases in magnitude as compared to the magnitude of the risk estimate when using the no exposure group as the referent. Importantly, however, the low exposure group contained only a small number of individuals (n=12) making this estimate very uncertain. No evidence of a significant positive association between stomach cancer and methyl bromide use was observed in any other tertile with the low exposure group as the referent or in any tertile with the no exposure group as the referent. Similarly, no evidence of a significant positive association between stomach cancer and methyl bromide use was observed (in any tertile) in the age-adjusted analysis with the no exposure group as the referent. And, no evidence of a significant positive association for methyl bromide exposure and stomach cancer, based on ever/never methyl bromide exposure (OR = 1.01, 95% CI: 0.59, 1.74). Pesticide exposure assessment was semi-ecological in nature and there was potential for misclassification of the pesticide exposure as the analysis was limited by having only county-level information on growers (crop type, month, and county, and pounds of pesticide applied based on Pesticide Use Reports) to determine pesticide exposure for each worker.

Overall, there is limited, but insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and stomach cancer. While Barry et al. (2012) reported evidence of strong positive association, the findings are based on only a small number of exposed cases and warrant further examination in the AHS cohort and other agricultural populations. Similarly, Mills and Yang (2007) also reported evidence of a positive association, but assessed exposure ecologically using county-level methyl bromide use information.

o For colon cancer, Barry et al. (2012) reported evidence of a positive association with methyl bromide only in their low exposure group for intensity-weighted lifetime days

of exposure but no evidence of a significant positive association for any other exposure category or dose-response relationship. An earlier AHS study by Lee et al. (2007) also reported no evidence of a significant positive association between methyl bromide exposure and colon cancer in an ever-never analysis. Given the mixed findings, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and colon cancer.

- o For lymphohematopoietic cancers considered collectively, Barry et al. (2012) reported evidence of a positive association with methyl bromide only in their low exposure group for intensity-weighted lifetime days of exposure but no evidence of a significant positive association for any other exposure category or dose-response relationship. As such, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and lymphohematopoietic cancers.

- o For NHL, two studies Barry et al. (2012) and Alavanja et al. (2014) investigated the association between methyl bromide and NHL among AHS participants. Barry et al. (2012) reported evidence of a moderately strong association with methyl bromide only in their low exposure category for intensity-weighted lifetime days of exposure and no evidence of a positive association for any other exposure category for intensity-weighted lifetime days of exposure or dose-response relationship. A second study (Alavanja et al. 2014) investigated methyl bromide exposure and NHL and NHL subtypes among AHS participants and extended the follow-up period. For NHL overall, authors reported a moderately strong positive association for the low exposure category of lifetime days of exposure to methyl bromide and a positive association for the low exposure category for intensity-weighted days of exposure to methyl bromide, but no other significant positive associations were noted for either the medium or high exposure categories for either lifetime days of exposure or intensity-weighted days. Given that the mixed finding, with positive associations observed in low exposure groups but not higher exposure categories, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and NHL and NHL subtypes.

Non-Carcinogenic Effects

- AHS studies reported no evidence of a significant positive association between methyl bromide exposure and thyroid disease, Parkinson's disease, dream enacting behavior, eye disorders, suicide, depression, amyotrophic lateral sclerosis, rheumatoid arthritis, myocardial infarction, renal disease, diabetes, fatal injury, stroke, asthma, wheeze, and rhinitis.

- For chronic bronchitis, two cross-sectional studies evaluated the relationship with methyl bromide among the AHS cohort. Valcin et al. (2007) reported evidence of a positive association between methyl bromide exposure and chronic bronchitis among female spouses of pesticide applicators, based on lifetime use, controlling for age and state. In contrast, Hoppin et al. (2007) reported no evidence of a positive association between chronic bronchitis and methyl bromide exposure among male pesticide applicators, based on ever/never use. The cross-sectional design of each of these studies decreases the

reliability of the results, as temporality could not be determined. Given the mixed findings and cross-sectional design of both studies, there is insufficient evidence at this time to conclude that a clear associative or causal relationship exists between methyl bromide and chronic bronchitis.

In summary, the epidemiological evidence is insufficient at this time to conclude that a clear associative or causal relationship exists between methyl bromide and the carcinogenic and non-carcinogenic health outcomes in the studies reported here. Early, strong associations with prostate cancer dissipated over time, perhaps due to decreasing prevalence of use of methyl bromide in the AHS cohort, as noted by the study authors. While Barry et al. (2012) reported evidence of strong positive and monotonically increasing association between methyl bromide and stomach cancer, the findings are based on only a small number of exposed cases and warrant further examination in the AHS cohort and other agricultural populations. Similarly, Mills and Yang (2007) also reported evidence of a positive association between methyl bromide exposure and stomach cancer in a (separate) population of California farm workers, they assessed exposure ecologically using county-level methyl bromide use information and this association was only observed when the (small) low exposure group was used as the referent and disappeared when the substantially larger no-exposure group was used as the referent.

IV.   CONCLUSIONS

On December 1, 2012 the final phase EPA-required new safety measures for soil fumigant pesticides (chloropicrin, dazomet, metam sodium/potassium, and methyl bromide) went into effect. These safety measures are required to increase protection for agricultural workers and bystanders.

In the current IDS analysis from January 1, 2013, to September 14, 2018, there were seven incidents in Main IDS that involved the active ingredient methyl bromide. One incident involved an equipment failure that released methyl bromide resulting in the death of a worker. Two of the incidents were classified as major severity and four of the incidents were classified as moderate severity. These cases are described in Appendix A. In Aggregate IDS, four minor severity incidents were reported. In SENSOR-Pesticides from 2010-2015, 34 cases involving methyl bromide were identified. Thirty two percent of methyl bromide cases reported to SENSOR-Pesticides (2010-2015) involved exposure from tarp rip/tears or tarp handling activities.

A review of the year-by-year incidents over time in IDS shows that there were very few methyl bromide incidents reported both pre- and post- (2012) mitigation; however, there appears to be a slight decrease in the number methyl bromide incidents reported SENSOR-Pesticides since the 2012 mitigation was implemented. While there were still some severe incidents and one fatality reported involving methyl bromide, the frequency of methyl bromide incidents reported to both datasets has remained low over time.

Regarding epidemiology, overall, we considered the epidemiological evidence to be insufficient at the time to conclude that a clear associative or causal relationship exists between methyl bromide exposure and the carcinogenic and non-carcinogenic health outcomes assessed in the

studies reported here. The Agency will continue to monitor the epidemiology data as it accumulates, and – if a concern is triggered – additional analysis will be conducted.

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Methyl Bromide Incidents Reported to Main IDS from January 1, 2013, to September 14, 2018						
Incident Package Report	Incident Date	Location	Reg Number	Ingredient Name	Exposure Severity	Incident Description
025770 – 00010	9/19/2013	CA	011220-00010	Methyl bromide, Chloropicrin	Moderate, Minor	Fourteen field workers entered a field and began to harvest lettuce. 10 employees began to experience burning eyes, headache, throat irritation, and nausea. They had been working in the outer buffer zone of a methyl bromide application to strawberries two days prior at a site catty-corner to the lettuce field. Five individuals were taken to receive medical treatment.
026994 – 00014	8/28/2014	CA		Methyl bromide	Moderate	67 fieldworker who were harvesting cane berries inside "hoop houses" while a helicopter made an application to an adjacent celery field. Eight worker experienced symptoms.
027146 – 00008	8/28/2014	CA	005785-00024	Chloropicrin, Methyl bromide	Moderate	An employee handler was working during a field fumigation of Terr-O-Gas 67, EPA Reg. No. 5785-24. His duties consisted of shoveling dirt on the ends of the tarps when the applicator finished his round, and to assist in any needed tarp repairs. The application was completed late morning without incident by Soil-Fume. As afternoon winds developed the tarps tore in several places. The employee was outside of the field cleaning his respirator at the time. He entered the treated field to help repair the tarps putting the respirator on as he crossed the treated field. He noted he could feel air leaking past his cheek into the mask. At that moment he felt he could not get his breath, so he removed his respirator and ran out of the treated part of the field. He had difficulty breathing, was coughing, and vomited several times. Other symptoms included dizziness and headache. He rested for a short time and then returned to work. At the end of his shift, he complained to his supervisor of being sick, at which time, his supervisor took him to the hospital.
027530 – 00001	3/14/2015	CRUZ BAY, VI		Methyl bromide	Major	A family of four was poisoned by exposure to methyl bromide while vacationing in the Virgin Islands. They experienced seizures and inability to breathe. Three of the family members are in critical condition.
028317 - 00001	12/1/2015	NJ		Methyl bromide	Moderate	A pest control employee experienced a frostbite-type burn when using methyl bromide.
029252 - 00001	7/23/2016	GILMORE, CA	005785-00056	Methyl bromide	Major	This was an industrial workplace accident. An employee working in a pesticide handling facility was exposed to liquid methyl bromide 98% (2% chloropicrin) while assisting in the connection of a dry-cam valve to a railcar material transfer line. Two employees were engaged in the activity.

Methyl Bromide Incidents Reported to Main IDS from January 1, 2013, to September 14, 2018						
Incident Package Report	Incident Date	Location	Reg Number	Ingredient Name	Exposure Severity	Incident Description
						While reconnecting the dry-cam valve, it failed and liquid sprayed from the transfer line onto one employee's body (waist-down). He sustained severe burns on his legs, ankles and feet. He was in the hospital for four weeks and received skin grafts.

Appendix B: Table of Included AHS Studies

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses
Alavanja et al. 2003	Cohort study Males only	High-quality questionnaire answered at enrollment regarding pesticide use	State cancer registries	Adjusted for family history of prostate cancer and age	Unconditional logistic regression was used to obtain OR and 95% CI
Alavanja et al. 2014	Cohort study	High-quality questionnaire answered at enrollment and follow-up regarding pesticide use	State cancer registries	Adjusted for age, race, state of residence, and herbicide use	Poisson regression model was used to obtain RR and 95% CI
Andreotti, G. et al. 2010					
Barry et al. 2011	Population-based case-control study White males only	Self-administered questionnaire to obtain detailed information on farm activities and use of pesticides at enrollment and take-home	State cancer registries	Adjusted for state of residence and age	Unconditional logistic regression to obtain OR and 95% CI; a small number of exposed cases
Barry et al. 2012	Cohort study	Self-administered questionnaire to obtain detailed information on farm activities and use of pesticides at enrollment and take-home	State cancer registries	Adjusted for age, gender, race, state, applicator type, enrollment year, smoking, alcohol use, education, family history of cancer, correlated pesticides	Poisson regression to obtain RR and 95% CI
Beard et al. 2011	Cohort study	High-quality questionnaire answered at enrollment regarding past pesticide use	State mortality files and the National Death Index	Adjusted for age, sex, number of children, frequency of alcohol consumption within the past year, and smoking	Cox proportional hazards model was used to obtain HR and 95% CI

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses
Beard et al. 2013	Cohort study	Self-administered questionnaire at enrollment for spouses of enrolled applicators obtaining farm exposures, general health information, and reproductive health history	Self-reported responses by cases during follow-up telephone interview	Adjusted for education level, age at enrollment, ever diagnosed with diabetes, state of residence, and drop out, as well as to account for number of study subjects who were did not complete the follow-up interview	Log-binomial regression to obtain RR and 95% CI
Beard et al. 2014	Case-control study Males only	Two self-administered questionnaires at enrollment and follow-up regarding past pesticide exposure	Self-reported physician-diagnosis by cases	Adjusted for confounders including age, diabetes diagnosis, education level, and state of residence, as well as missing covariate data and study drop-outs	Polytomous logistic regression was used to obtain OR and 95% CI
Bonner et al. 2017	Cohort study	High-quality questionnaire answered at enrollment and at home shortly following enrollment	State cancer registries identifying lung cancer	Adjusted for smoking (pack years), gender, total lifetime pesticide use, and age	Cox proportional hazards model was used to obtain HR and 95% CI
Dayton et al. 2010	Cohort study Farm women	High-quality questionnaire answered at home shortly following enrollment, and followed-up via a phone interview	Self-reported MI	Adjusted for age, BMI, smoking status, state of residence	Logistic regression to obtain OR and 95% CI

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Engel et al. 2005	Cohort study Women only	Take-home questionnaire from spouses of enrolled applicators obtaining farm exposures, general health information, and reproductive health history; information obtained from applicators used as measure of possible indirect exposure to spouses	State cancer registries identifying malignant breast cancer	Adjusted for age, race and state; evaluated BMI, age at menarche, parity, age at first birth, menopausal status, age at menopause, family history of breast cancer, physical activity, smoking, alcohol consumption, fruit and vegetable consumption and education but none found to be significant	Poisson regression to obtain RR and 95% CI
Goldner et al. 2010	Cross-sectional study Female spouses of male farmers	High-quality questionnaires (at enrollment and follow-up) answered by subjects in AHS cohort regarding occupational pesticide use histories	Self-reported physician diagnosis	Adjusted for BMI, age at enrollment, smoking status, hormone replacement therapy (ever/never), and education	Polytomous logistic regression to obtain OR and 95% CI
Goldner et al. 2013	Cohort study Male pesticide applicators	High-quality questionnaires (at enrollment and follow-up) answered by subjects in AHS cohort regarding occupational pesticide use histories	Self-reported physician diagnosis	Adjusted for BMI, age at enrollment, and education	Logistic regression to obtain OR and 95% CI
Henneberger et al. 2014	Cross-sectional study	High-quality questionnaires (at enrollment and take-home) answered by subjects in AHS cohort regarding occupational pesticide use histories	Self-reported a physician diagnosis of asthma	Adjusted for age, ever smoked, allergic status, state, adult onset asthma, indicator variables for current and past exposures	Logistic regression to obtain OR and 95% CI
Hoppin et al. 2002	Cross-sectional study	High-quality questionnaires answered by subjects at enrollment and at follow-up in AHS cohort regarding	Self-reported wheeze	Adjusted for age, state, past smoking, current smoking, and asthma/atopy	Base logistic regression to obtain OR and 95% CI

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses
		occupational pesticide use histories			
Hoppin et al. 2006	Cross-sectional study	High-quality questionnaires answered by subjects at enrollment and at follow-up in AHS cohort regarding occupational pesticide use histories	Self-reported wheeze	Adjusted for age, smoking, BMI	Base logistic regression to obtain OR and 95% CI
Hoppin et al. 2007	Cross-sectional study	High-quality questionnaires answered by subjects at enrollment and at follow-up in AHS cohort regarding past pesticide use	Self-reported chronic bronchitis	Adjusted for age, state, gender, and pack years of smoking	Base logistic regression to obtain OR and 95% CI
Hoppin et al. 2008 Farm women	Cross-sectional study	Self-reported questionnaire or telephone interview at study enrollment (1993 – 1997), detailing pesticide usage and whether they had received a physician's diagnosis of asthma	Self-reported physician diagnosed asthma	Adjusted for age, state, smoking status, BMI, and whether or not the subject had grown up on a farm	Polytomous logistic regression was used to calculate OR and 95% CI
Hoppin et al. 2009 Males only	Cross-sectional study	High-quality questionnaires answered by subjects in AHS cohort regarding past pesticide use at enrollment and via a postal questionnaire	Self-reported physician diagnosed asthma	Adjusted for age, state, smoking, BMI, and high pesticide exposure events (pesticide poisoning)	Polytomous logistic regression was used to calculate OR and 95% CI
Kamel et al. 2007	Cross-sectional study	High-quality self-administered questionnaires at study enrollment and during the follow-up telephone interview (5 years later) regarding past pesticide use	Self-reported, physician-diagnosis of Parkinson's disease	Adjusted for age, state, and type of participant (applicator or spouse)	Hierarchical logistic regression was used to calculate OR and 95% CI
Kamel et al. 2012	Prospective cohort study	High-quality self-reported questionnaire completed at study enrollment	Self-reported ALS	Adjusted for age and gender	Unconditional logistic regression model was used to

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					calculate RR and 95% CI
Kirrane et al. 2005	Cross-sectional study Females spouses of pesticide applicators	A postal questionnaire was initially mailed, and follow-up telephone interviews were conducted for those didn't return the original questionnaire via mail	Self-reported eye disorders	Adjusted for age and state of residence	Logistic regression was used to calculate OR and 95% CI
Koutros et al. 2011	Nested case-control study Males only	High-quality questionnaires answered by subjects at enrollment and at follow-up telephone interview (1999 - 2003) in AHS cohort regarding past pesticide exposure	State cancer registries	Adjusted for state, age, and family history of prostate cancer	Unconditional logistic regression was used to calculate OR and 95% CI
Koutros et al. 2013	Prospective cohort study Males only	High-quality questionnaires answered by subjects at enrollment and at home shortly after enrollment in AHS cohort regarding past pesticide use	State cancer registries	Adjusted for family history of prostate cancer, age, state, race, smoking, fruit servings, and leisure time physical activity in winter	Poisson regression analysis was used to calculate RR and 95% CI
Koutros et al. 2016	Prospective cohort study Males only	High-quality questionnaires answered by subjects at enrollment and at follow-up (5 years later) in AHS cohort regarding past pesticide exposure	State cancer registries	Moderate control for confounders. Adjusted for race, age, pack-years of cigarette smoke, state of residence, and pipe smoking	Poisson regression analysis was used to calculate RR and 95% CI
Lebov et al. 2015	Cohort study Female spouses of pesticide applicators	Self-administered questionnaires completed at enrollment and at home regarding past pesticide usage (included frequency and duration info.)	Cases were ascertained via the U.S. Renal Data System	Adjusted for age	Cox proportional hazards model was used to obtain HR and 95% CI
Lebov et al. 2016	Cohort study	Self-administered questionnaires completed at enrollment and at	Cases were ascertained via	Adjusted for state of study enrollment	Cox proportional hazards model to

Journal Article	Study Design	Exposure Assessment	Outcome Assessment	Confounder Control	Statistical Analyses
	Male pesticide applicators	home regarding past pesticide usage	a national database		obtain HR and 95% CI
Lee et al. 2007	Prospective cohort study	High-quality initial questionnaire answered, followed by a more detailed follow-up self-administered questionnaire completed at home	State death registries and the National Death Index identifying colorectal cancer	Adjusted for smoking, age, state, and total days of pesticide application among enrolled subjects	Unconditional multivariate logistic regression was used to calculate OR and 95% CI
Lerro et al. 2017	Cohort study Male pesticide applicators	Self-administered questionnaires completed at enrollment and at follow-up regarding past pesticide usage (included frequency and duration info.)	Serum samples were collected and measured to confirm disease	Adjusted for age, smoking, state, BMI, and correlated pesticides	Logistic regression was used to calculate OR and 95% CI
Meyer et al. 2017	Prospective cohort study Male pesticide applicators	Self-administered questionnaires completed at enrollment and at follow-up regarding past pesticide usage	Self-reported or physician diagnosed RA	Adjusted for age, pack years smoking, education and state of enrollment	Logistic regression was used to calculate OR and 95% CI
Mills et al. 2009	Prospective cohort study Male pesticide applicators	Two self-reported high-quality questionnaires completed at study enrollment and again at the 5-year follow-up regarding past pesticide use	State and national death databases	Moderate adjustment. Adjusted for age, smoking, and state (fatal MI), state, age, smoking, and BMI (non-fatal MI)	Cox proportional hazard regression model to obtain HR and 95% CI
Montgomery et al. 2008	Prospective cohort study	High-quality questionnaires provided at enrollment, take-home, and during the follow-up interview regarding past pesticide exposures	Self-reported incident diabetes	Adjusted for age, BMI, and state of residence	Logistic regression was used to calculate OR and 95% CI
Montgomery et al. 2017	Nested case-control study	High-quality questionnaires provided at enrollment and at	Cases ascertained by physicians	Adjusted for age, gender, and smoking	Multivariable logistic regression was used to

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		follow-up regarding past pesticide exposures			calculate OR and 95% CI
Rinsky et al. 2013	Prospective cohort study Males only	High-quality initial questionnaire answered by study subjects in AHS at enrollment, followed by a more detailed follow-up self-administered questionnaire completed at home	State death certificates	Adjusted for smoking status, alcohol intake, and state	Cox proportional hazard regression model to obtain HR and 95% CI
Shrestha et al. 2018a	Prospective cohort study Female spouses only	High-quality questionnaires provided at enrollment	Self-reported outcome validated via medical records	Adjusted for education, state, smoking, and correlated pesticides	Cox proportional hazard regression model was used to calculate HR and 95% CI
Shrestha et al. 2018b	Prospective cohort study Male pesticide applicators only	High-quality questionnaires provided at enrollment	Self-reported outcome validated via medical records	Adjusted for education, state, smoking, and correlated pesticides	Cox proportional hazard regression model was used to calculate HR and 95% CI
Shrestha et al. 2018c	Prospective cohort study	Pesticide use information collected at enrollment and up to two follow-up interviews.	Self-reported DEB	Adjusted for age, smoking, alcohol consumption, marital status, education, state, and head injury	Multivariable logistic regression was used to calculate OR and 95% CI
Slager et al. 2009	Cross-sectional study	High-quality initial questionnaire answered, followed by a more detailed follow-up self-administered questionnaire completed at home	Self-reported rhinitis	Adjusted for age, education, and growing up on a farm	Logistic regression was used to calculate OR and 95% CI
Starling et al. 2014	Prospective cohort study	Pesticide use information collected at enrollment and up to two follow-up interviews	Self-reported incident diabetes	Adjusted for BMI and state of residence	Cox proportional hazard regression model was used to calculate HR and 95% CI

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Valcin et al. 2007	Cross-sectional study Female spouses of pesticide applicators	High-quality questionnaires answered by subjects in AHS cohort regarding past pesticide exposures	Self-reported physician diagnosis	Adjusted for age and state	Logistic regression to obtain OR and 95% CI
Waggoner et al. 2013	Prospective cohort study	Self-administered questionnaires at enrollment and follow-up that were used to collect information on pesticide use	State death registries and the National Death Index	Adjusted for age and state	Cox proportional hazards model to calculate HR and 95% CI